



# **STIC Search Report**

## **Biotech-Chem Library**

**STIC Database Tracking Number:** 122453

**TO: Devesh Khare**  
**Location: rem/5c35/5c18**  
**Art Unit: 1623**  
**Wednesday, May 19, 2004**

**Case Serial Number: 10/618148**

**From: Mary Jane Ruhl**  
**Location: Biotech-Chem Library**  
**Remsen 1-B55**  
**Phone: 571-272-2524**

**maryjane.ruhl@uspto.gov**

### **Search Notes**

Examiner Khare,

Here are the results for your recent search request.

Please feel free to contact me if you have any questions about these results.

Thank you for using STIC services. We appreciate the opportunity to serve you.

Sincerely,

Mary Jane Ruhl  
Technical Information Specialist  
STIC  
CM-1, Rm. 6-A-06  
605-1155



# STIC SEARCH RESULTS FEEDBACK FORM

## Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact*:

Mary Hale, Information Branch Supervisor  
571-272-2507 Remsen E01 D86

## Voluntary Results Feedback Form

➤ I am an examiner in Workgroup:  Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature  
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library Remsen Bldg.



STIC-Biotech/ChemLib

122453

122531

mej

From: Khare, Devesh  
Sent: Wednesday, May 19, 2004 10:54 AM  
To: STIC-Biotech/ChemLib  
Subject: Search Req. for 10/618,148. Claims attached. Thank you.



SEARCH.REQ1.doc



claims.doc

Searcher: \_\_\_\_\_  
Phone: \_\_\_\_\_  
Location: \_\_\_\_\_  
Date Picked Up: \_\_\_\_\_  
Date Completed: \_\_\_\_\_  
Searcher Prep/Review: \_\_\_\_\_  
Clerical: \_\_\_\_\_  
Online time: \_\_\_\_\_

TYPE OF SEARCH:  
NA Sequences: \_\_\_\_\_  
AA Sequences: \_\_\_\_\_  
Structures: \_\_\_\_\_  
Bibliographic: \_\_\_\_\_  
Litigation: \_\_\_\_\_  
Full text: \_\_\_\_\_  
Patent Family: \_\_\_\_\_  
Other: \_\_\_\_\_

VENDOR/COST (where applic.)  
STN: \_\_\_\_\_  
DIALOG: \_\_\_\_\_  
Questel/Orbit: \_\_\_\_\_  
DRLink: \_\_\_\_\_  
Lexis/Nexis: \_\_\_\_\_  
Sequence Sys.: \_\_\_\_\_  
WWW/Internet: \_\_\_\_\_  
Other (specify): \_\_\_\_\_

Access DB# 122453  
122531

## SEARCH REQUEST FORM

### Scientific and Technical Information Center

Requester's full Name: Devesh Khare Examiner #: 77931 Date: 05/19/2004  
Art Unit: 1623 Phone Number 272-0653 Serial Number: 10/618,148  
Mail Box: Remsen 5C18 and Bldg/Room Location: 5C35 Results Format Preferred (circle): PAPER DISK E-MAIL

### If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be search Include the elected species or structures, key words, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: See Bib Data Sheet on e-

dan.

Inventors (please provide full names): See Bib Data Sheet on e-

dan.

Earliest priority Filing Date: 7-10-2003

*\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please carry out a search on the following claims:

Please see the attached sheet for the claims.

Thank you.

.....

Thank you.

#### STAFF USE ONLY

Searcher: \_\_\_\_\_  
Searcher Phone #: \_\_\_\_\_  
Searcher Location: \_\_\_\_\_  
Date Searcher Picked Up: \_\_\_\_\_  
Date Completed: \_\_\_\_\_  
Searcher Prep & Review Time: \_\_\_\_\_  
Clerical prep time: \_\_\_\_\_  
On Line Time \_\_\_\_\_

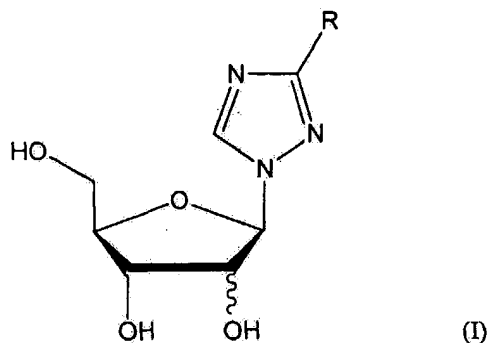
#### Type of Search

NA Sequence (#) \_\_\_\_\_  
AA Sequence (#) \_\_\_\_\_  
Structure (#) \_\_\_\_\_  
Bibliographic \_\_\_\_\_  
Litigation \_\_\_\_\_  
Fulltext \_\_\_\_\_  
Patent Family \_\_\_\_\_  
Other \_\_\_\_\_

#### Vendors and cost where applicable

STN \_\_\_\_\_  
Dialog \_\_\_\_\_  
Questel/Orbit \_\_\_\_\_  
Dr. Link \_\_\_\_\_  
Lexis/Nexis \_\_\_\_\_  
Sequence Systems \_\_\_\_\_  
WWW/Internet \_\_\_\_\_  
Other (specify) \_\_\_\_\_

1. A method of treatment or prophylaxis of an inflammatory bowel disease in a subject in need of said treatment or prophylaxis, said method comprising:
  - providing one or more ribofuranose derivatives having the Formula (I):



- wherein R is a group selected from the group consisting of a carboxamide, an amidine and pharmaceutically acceptable acid addition salts thereof and the configuration at the C<sub>2</sub> carbon of the ribofuranose moiety is D or L; and
- administering said one or more ribofuranose derivatives to said subject in an amount effective to treat or prevent said inflammatory bowel disease.

2. The method of claim 1, wherein the ribofuranose derivative having the Formula (I) comprises at least one derivative selected from the group consisting of 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, 1-β-L-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-amidine, 1-β-L-ribofuranosyl-1H-1,2,4-triazole-3-amidine, pharmaceutically acceptable acid addition salts thereof.
3. The method of claim 2, wherein the ribofuranose derivative having Formula (I) is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide.

=> d his ful

FILE 'REGISTRY' ENTERED AT 16:30:38 ON 19 MAY 2004

L29 STR  
L30 0 SEA SSS SAM L29  
L31 1 SEA SSS FUL L29

FILE 'HCAPLUS' ENTERED AT 16:39:28 ON 19 MAY 2004

L32 1 SEA ABB=ON L31

FILE 'REGISTRY' ENTERED AT 16:40:14 ON 19 MAY 2004

L33 STR L29  
L34 0 SEA SSS SAM L33  
L35 1 SEA SSS FUL L33  
E RIBOFURANOSE/CN  
L36 STR L33  
L37 6 SEA SSS SAM L36  
L38 127 SEA SSS FUL L36

FILE 'HCAPLUS' ENTERED AT 16:42:38 ON 19 MAY 2004

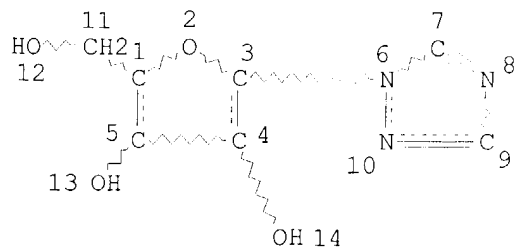
L39 1951 SEA ABB=ON L38  
L40 1 SEA ABB=ON L39 AND ?INFLAM?(W)?BOWEL?  
L41 6 SEA ABB=ON L39 AND (?INFLAM?(W)(?BOWEL? OR ?CROHN?) OR  
?ULCER?(W)?COLITIS?)

*127 compds from Registry - see  
6 one stat for  
structure*

*6 cite from CA Plus*

*All include 1-β-D-ribofuranosyl-1-H-1,2,4-  
triazole-3-carboxamide - Claim 3.*

=> d que stat 141  
L36 STR



NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE

L38 127 SEA FILE=REGISTRY SSS FUL L36  
L39 1951 SEA FILE=HCAPLUS ABB=ON L38  
L41 6 SEA FILE=HCAPLUS ABB=ON L39 AND (?INFLAM?(W) (?BOWEL? OR  
?CROHN?) OR ?ULCER?(W) ?COLITIS?)

=&gt; d ibib abs hitstr 141 1-6

L41 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:331903 HCAPLUS

DOCUMENT NUMBER: 140:337930

TITLE: Anti-CD20 antibody-drug conjugates for the treatment of cancer and immune disorders in mammal and human

INVENTOR(S): Wahl, Alan F.; Senter, Peter D.; Law, Che-leung; Cervený, Charles G.

PATENT ASSIGNEE(S): Seattle Genetics, Inc., USA

SOURCE: PCT Int. Appl., 161 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004032828	A2	20040422	WO 2003-US23895	20030730
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-400404P P 20020731

AB The present invention relates to methods and compns. for the treatment of CD20-expressing cancers and immune disorders involving CD20-expressing cells. The present methods comprise administering to a subject an anti CD20 antibody-drug conjugate that has a high potency and/or is capable of internalizing into CD20-expressing cells. The present invention further provides pharmaceutical compns. and kits comprising such conjugates. The present invention yet further provides methods of and compns. relating to combination therapy of cancer and immune disorders involving CD20-expressing cells using the anti-CD20 antibody-drug conjugates of the invention.

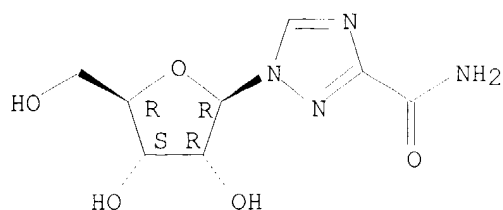
IT **36791-04-5D**, Ribavarin, conjugates with anti-CD20 antibody  
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anti-CD20 antibody-drug conjugates for the treatment of cancer and immune disorders in mammal and human)

RN 36791-04-5 HCAPLUS

CN 1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





L41 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2003:301196 HCAPLUS  
 DOCUMENT NUMBER: 138:297636  
 TITLE: Use of STAT-6 inhibitors as therapeutic agents  
 INVENTOR(S): Carson, Dennis A.; Cottam, Howard B.; Leoni, Lorenzo  
 M.; Barchechath, Sylvie  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA  
 SOURCE: PCT Int. Appl., 62 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031587	A2	20030417	WO 2002-US32503	20021009
WO 2003031587	A3	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG US 2003143199 A1 20030731 US 2002-269110 20021009 PRIORITY APPLN. INFO.: US 2001-328162P P 20011009 US 2001-328689P P 20011010				

OTHER SOURCE(S): MARPAT 138:297636

AB The invention provides therapeutic method to enhance the efficacy of interferon treatment comprising administering to a mammal subject to interferon treatment a compound which is an antagonist of the IL-4 or IL-13 signal transduction pathway in an amount effective to enhance said efficacy. The method includes treatment of diseases such as cancer, proliferative fibrotic diseases, viral diseases, or autoimmune diseases. The invention also includes the use of chemotherapeutic agents, radiation or other treatments in conjunction with the method of the invention.

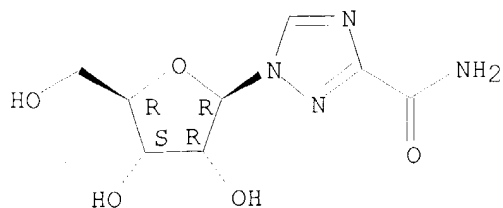
IT **36791-04-5**, Ribavirin

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (use of STAT-6 inhibitors as therapeutic agents)

RN 36791-04-5 HCAPLUS

CN 1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L41 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:202634 HCAPLUS

DOCUMENT NUMBER: 138:238191

TITLE: Preparation of 1-[1-(pyrimidin-5-ylcarbonyl)piperidin-4-yl]piperidin-4-amines as CCR5 antagonists

INVENTOR(S): Palani, Anandan; Miller, Michael W.; Scott, Jack D.

PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: PCT Int. Appl., 105 pp.

CODEN: PIXXD2

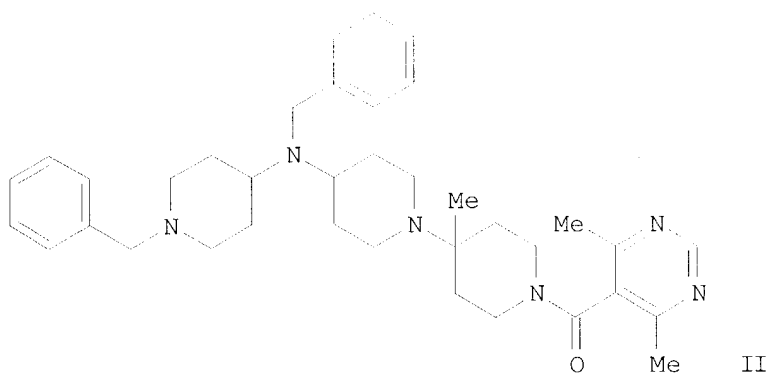
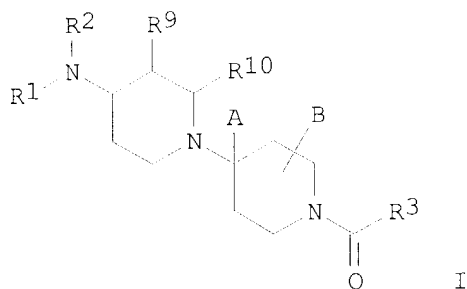
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020716	A1	20030313	WO 2002-US27389	20020828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004010008	A1	20040115	US 2002-229466	20020828
US 2004092745	A1	20040513	US 2003-628933	20030729
US 2004092551	A1	20040513	US 2003-629466	20030729
PRIORITY APPLN. INFO.:			US 2001-315683P	P 20010829
			US 2002-229466	A3 20020828
OTHER SOURCE(S):		MARPAT 138:238191		
GI				



AB The title compds. [I; R1 = piperidiny1, Ph, etc.; R2 = CH2Ph, 4-pyridylmethyl, etc.; R3 = 4,6-dimethylpyrimidine-5-yl, Ph, etc.; R9, R10, B = H, alkyl, haloalkyl; A = H, alkyl, alkenyl] and their pharmaceutically acceptable salts, useful, alone or in combination with another agent, in the treatment of Human Immunodeficiency Virus (HIV), solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, **inflammatory bowel** disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis, were prepared E.g., a 6-step synthesis of II, starting from 4-hydroxypiperidine and N-Boc-4-piperidone, which showed IC50 of 1.7 nM in luciferase HIV replication assay, was given.

IT **36791-04-5**, Ribavirin

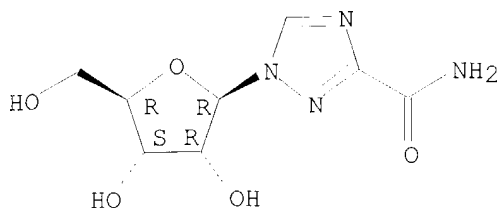
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of 1-[1-(pyrimidin-5-ylcarbonyl)piperidin-4-yl]piperidin-4-amines as CCR5 antagonists)

RN 36791-04-5 HCAPLUS

CN 1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

## RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:449662 HCAPLUS

DOCUMENT NUMBER: 137:33310

TITLE: Preparation of anilinopyrimidines as IKK inhibitors

INVENTOR(S): Kois, Adam; MacFarlane, Karen J.; Satoh, Yoshitaka; Bhagwat, Shripad S.; Parnes, Jason S.; Palanki, Moorthy S. S.; Erdman, Paul E.

PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 194 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

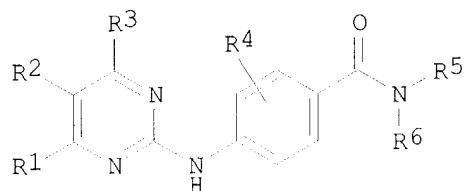
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046171	A2	20020613	WO 2001-US46403	20011205
WO 2002046171	A3	20030123		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003203926	A1	20031030	US 2001-4642	20011204
AU 2002020195	A5	20020618	AU 2002-20195	20011205
EP 1349841	A2	20031008	EP 2001-999564	20011205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-251816P P 20001206  
WO 2001-US46403 W 20011205

OTHER SOURCE(S): MARPAT 137:33310

GI



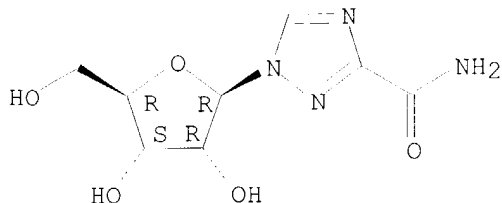
I

AB The title compds. [I; R1 = (un)substituted (hetero)aryl; R2 = H; R3 = H, alkyl; R4 = halo, OH, alkyl, alkoxy; R5, R6 = R8, (CH2)aCOR9, (CH2)aCO2R9, etc.; or NR5R6 = (un)substituted heterocycle; R8, R9 = H, alkyl, aryl, etc.; a = 0-4] having activity as inhibitors of IKK, particularly IKK-2, were prepared E.g., a multi-step synthesis of I [R1 = 4-ClC6H4; R2-R6 = H] having an IC50 of  $\leq 1 \mu\text{M}$  in the IKK-2 enzyme assay, was given. Such compds. I have utility in the treatment of a wide range of conditions

that are responsive to IKK inhibition. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. containing one or more compds. of the above compds.

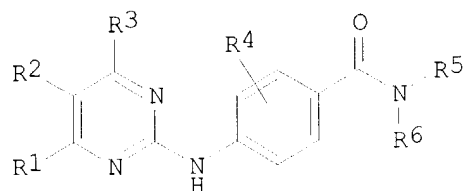
IT **36791-04-5**, Ribavirin  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anticancer agent; preparation of anilinopyrimidines as IKK inhibitors)  
 RN 36791-04-5 HCAPLUS  
 CN 1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.



L41 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2002:449661 HCAPLUS  
 DOCUMENT NUMBER: 137:33309  
 TITLE: Preparation of anilinopyrimidines as JNK pathway inhibitors  
 INVENTOR(S): Kois, Adam; MacFarlane, Karen J.; Satoh, Yoshitaka; Bhagwat, Shripad S.; Parnes, Jason S.; Palanki, Moorthy S. S.; Erdman, Paul E.  
 PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 199 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046170	A2	20020613	WO 2001-US46402	20011205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003220330	A1	20031127	US 2001-4645	20011204
AU 2002027214	A5	20020618	AU 2002-27214	20011205
EP 1349840	A2	20031008	EP 2001-996103	20011205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			US 2000-251904P	P 20001206
			WO 2001-US46402	W 20011205
OTHER SOURCE(S):			MARPAT 137:33309	
GI				



I

AB The title compds. [I; R1 = (un)substituted (hetero)aryl; R2 = H; R3 = H, alkyl; R4 = halo, OH, alkyl, alkoxy; R5, R6 = R8, (CH<sub>2</sub>)<sub>a</sub>COR9, (CH<sub>2</sub>)<sub>a</sub>CO<sub>2</sub>R9, etc.; or NR<sub>5</sub>R<sub>6</sub> = (un)substituted heterocycle; R8, R9 = H, alkyl, aryl, etc.; a = 0-4] having activity as inhibitors of the JNK pathway, were prepared E.g., a multi-step synthesis of I [R1 = 4-ClC<sub>6</sub>H<sub>4</sub>; R2-R6 = H] having an IC<sub>50</sub> of ≤ 10 μM in the JNK2 assay, was given. Such compds. I have utility in the treatment of a wide range of conditions that are responsive to inhibition of the JNK pathway. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. containing one or more compds. of the above compds.

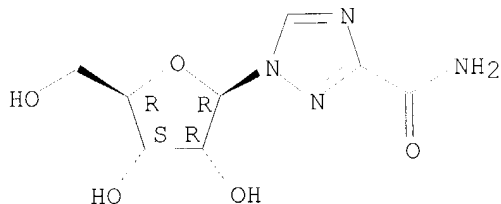
IT **36791-04-5**, Ribavirin

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anticancer agent; preparation of anilinopyrimidines as JNK pathway inhibitors)

RN 36791-04-5 HCAPLUS

CN 1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L41 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:635933 HCAPLUS

DOCUMENT NUMBER: 135:215973

TITLE: Use of peptide conjugates for enhancing drug delivery across biological membranes and tissues

INVENTOR(S): Rothbard, Jonathan B.; Wender, Paul A.

PATENT ASSIGNEE(S): Cellgate, Inc., USA

SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062297	A1	20010830	WO 2001-US4459	20010209
WO 2001062297	C2	20030109		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002009491 A1 20020124 US 2001-779693 20010207

EP 1263469 A1 20021211 EP 2001-909135 20010209

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2003523982 T2 20030812 JP 2001-561360 20010209

PRIORITY APPLN. INFO.:

US 2000-182166P P 20000214

US 2001-779693 A 20010207

WO 2001-US4459 W 20010209

AB This invention provides compns. and methods for enhancing delivery of drugs and other agents across a biol. barrier, including epithelial tissues such as the skin, gastrointestinal tract, pulmonary epithelium, and the like. The compns. and methods are also useful for delivery across endothelial tissues, including the blood brain barrier. The compns. and methods employ a delivery enhancing transporter that has sufficient guanidino or amidino sidechain moieties to enhance delivery of a compound across one or more layers of the tissue, compared to the non-conjugated compound. The delivery-enhancing polymers include, for example, poly-arginine mols. that are preferably between about 6 and 50 residues in length. Taxol conjugates with a heptamer of arginine was soluble in water in contrast with taxol itself. The conjugate was equally potent when assayed for biol. activity using standard cytotoxicity assay.

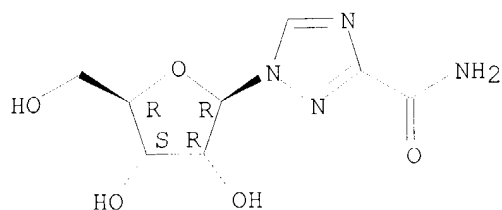
IT 36791-04-5, Ribavirin

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (use of peptide conjugates for enhancing drug delivery across biol. membranes and tissues)

RN 36791-04-5 HCAPLUS

CN 1H-1,2,4-Triazole-3-carboxamide, 1- $\beta$ -D-ribofuranosyl- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

8

THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs ind hitstr 128 1-15

L28 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:775951 HCAPLUS

DOCUMENT NUMBER: 134:80763

TITLE: Effect of opioid-active therapeutics on the ascending

reflex pathway in the rat ileum

AUTHOR(S): Allescher, H. D.; Storr, M.; Piller, C.; Brantl, V.; Schusdziarra, V.

CORPORATE SOURCE: Department of Internal Medicine II, Technical University of Munich, Munich, 81675, Germany

SOURCE: Neuropeptides (Edinburgh) (2000), 34(3&4), 181-186  
CODEN: NRPPDD; ISSN: 0143-4179

PUBLISHER: Harcourt Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB For a long time therapeutic agents that interact with opioid receptors have been used in antidiarrheal therapy. The action of the opioid active substances on motility and transit have already been characterized; however, their effects on myenteric reflexes and their possible luminal action have not yet been investigated. Loperamide, fedotozine and  $\beta$ -casomorphin-4, as well as the casomorphin-analog  $\beta$ -CM-4027, are, or have been, suggested as therapeutic agents and were studied in the isolated rat ileum for their effect on the ascending reflex pathway.  $\beta$ -CM-4027 > fedotozine > loperamide >  $\beta$ -casomorphin-4 caused a concentration-dependent inhibition of the ascending contractile reflex response with an IC<sub>50</sub> of  $1.4 \times 10^{-7}$ M,  $1.5 \times 10^{-6}$ M,  $4.1 \times 10^{-6}$ M and  $4.5 \times 10^{-6}$ M resp. At the same time as the oral contractile reflex response was inhibited, all four opioid agonists (CM-4027 >  $\beta$ -casomorphin-4 > fedotozine > loperamide) increased the latency of the reflex response. Both effects were blocked by naloxone, indicating the involvement of opioid receptors. These results demonstrate that opioid-active drugs and substances modify the peristaltic reflex by reducing the efficacy of the reflex response and modulating the timing of the reflex pathway. In a second series of expts., luminal application of opioid-active drugs was compared with serosal application.  $\beta$ -Casomorphine-4 caused a concentration-dependent inhibition of the oral reflex response with an IC<sub>50</sub> of  $3 \times 10^{-3}$ M which was 750 times higher than after serosal application. In contrast, a stable and highly selective kappa opioid agonist (U-50,488), which caused potent inhibition upon serosal application (IC<sub>50</sub>:  $2.3 \times 10^{-7}$ M), showed no inhibitory effect after luminal application up to a concentration of  $10^{-2}$ M. Thus casomorphins could have a local effect on the gut wall with no need for systemic absorption. This might be used for a possible therapeutic application.

CC 1-11 (Pharmacology)

ST antidiarrheal oral opioid peristaltic reflex ileum

IT **Intestine**

(ileum; opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT Drug delivery systems

(injections, i.v.; opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT Antidiarrheals

**Gastrointestinal** motility

(opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT Opioids

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES



(Uses)  
 (opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT Opioid receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (opioid-active therapeutics effect on ascending reflex pathway in ileum)

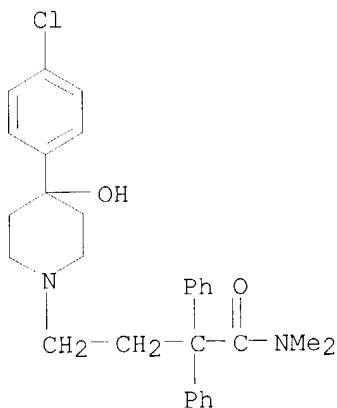
IT Drug delivery systems  
 (oral; opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT Reflex  
 (peristaltic; opioid-active therapeutics effect on ascending reflex pathway in ileum)

IT **53179-11-6**, Loperamide **74135-04-9**,  $\beta$ -Casomorphin-4 amide **98815-38-4** **123618-00-8**, Fedotozine  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (opioid-active therapeutics effect on ascending reflex pathway in ileum)

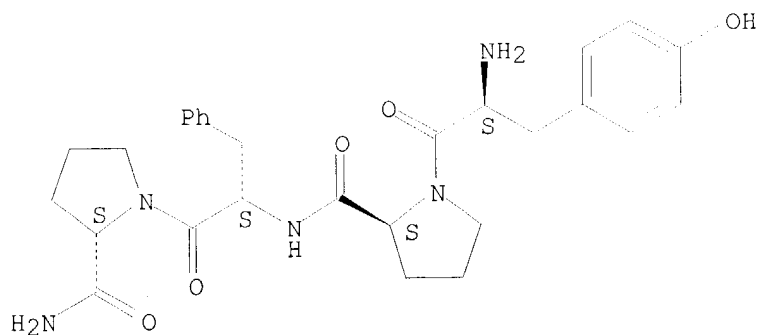
IT **53179-11-6**, Loperamide **74135-04-9**,  $\beta$ -Casomorphin-4 amide **98815-38-4** **123618-00-8**, Fedotozine  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (opioid-active therapeutics effect on ascending reflex pathway in ileum)

RN **53179-11-6** HCAPLUS  
 CN 1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- $\alpha,\alpha$ -diphenyl- (9CI) (CA INDEX NAME)



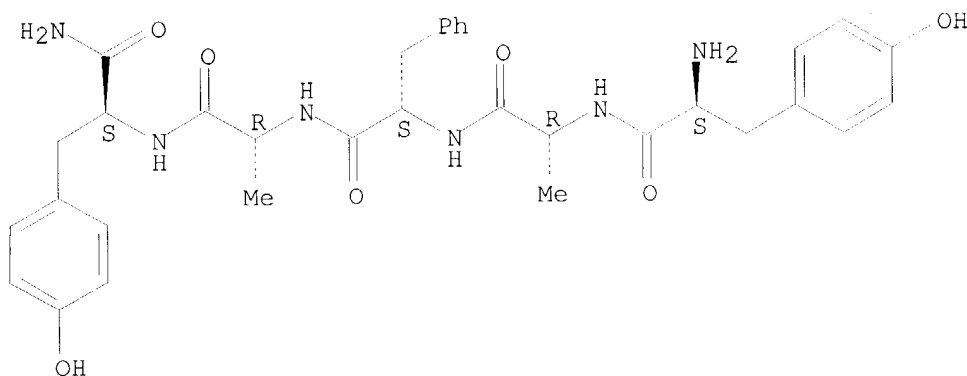
RN **74135-04-9** HCAPLUS  
 CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



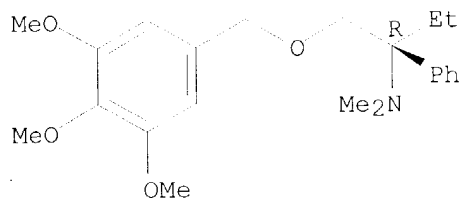
RN 98815-38-4 HCAPLUS  
 CN L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 123618-00-8 HCAPLUS  
 CN Benzenemethanamine,  $\alpha$ -ethyl-N,N-dimethyl- $\alpha$ -[[ (3,4,5-trimethoxyphenyl)methoxy]methyl]-, ( $\alpha$ R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

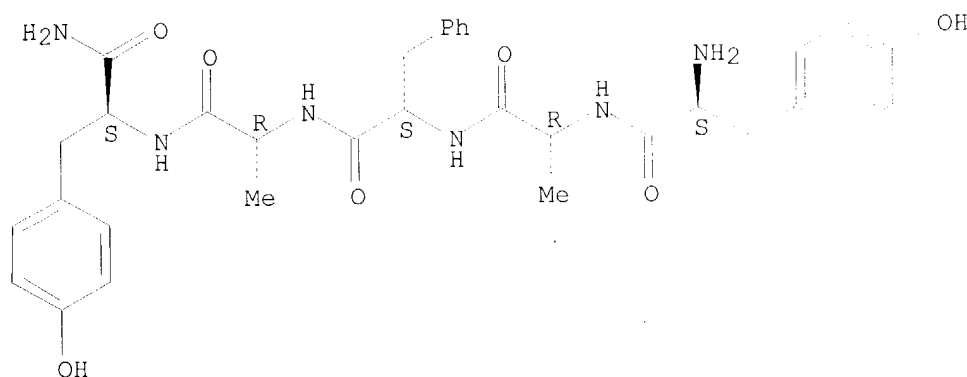


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2000:285550 HCAPLUS  
 DOCUMENT NUMBER: 133:84098  
 TITLE: Effects of oral casokefamide on plasma levels, tolerance, and **intestinal** transit in man  
 AUTHOR(S): Schulte-Frohlinde, E.; Reindl, W.; Bierling, D.;

Lersch, C.; Brantl, V.; Teschemacher, H.;  
Schusdziarra, V.  
CORPORATE SOURCE: Department of Medicine II, Technical University of  
Munich, Munich, 81675, Germany  
SOURCE: Peptides (New York) (2000), 21(3), 439-442  
CODEN: PPTDD5; ISSN: 0196-9781  
PUBLISHER: Elsevier Science Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Food-derived opioid peptides such as  $\beta$ -casomorphins are of interest  
for treatment of chronic diarrhea. The  $\beta$ -casomorphin analog  
casokefamide was administered orally at doses of 5.5, 8.0, and 16.0 mg to  
10 healthy male volunteers, resp. Dose-dependent increases of plasma  
levels with a maximum of 350 fmol/l were determined. No side-effects due to  
casokefamide has been observed. In comparison to placebo, casokefamide showed  
a trend toward prolongation of oro-caecal transit time. Orally applied  
casokefamide is well tolerated and may represent a useful tool for  
treatment of diarrhea in the future.  
CC 1-9 (Pharmacology)  
ST Section cross-reference(s): 2  
ST antidiarrheal casokefamide pharmacokinetics tolerance **intestinal**  
transit  
IT Antidiarrheals  
**Gastrointestinal** motility  
(effects of oral casokefamide on plasma levels, tolerance, and  
**intestinal** transit in man)  
IT **79805-24-6D**,  $\beta$ -Casomorphin, analogs **98815-38-4**,  
Casokefamide  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or  
effector, except adverse); BPR (Biological process); BSU (Biological  
study, unclassified); BIOL (Biological study); PROC (Process)  
(effects of oral casokefamide on plasma levels, tolerance, and  
**intestinal** transit in man)  
IT **79805-24-6D**,  $\beta$ -Casomorphin, analogs **98815-38-4**,  
Casokefamide  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or  
effector, except adverse); BPR (Biological process); BSU (Biological  
study, unclassified); BIOL (Biological study); PROC (Process)  
(effects of oral casokefamide on plasma levels, tolerance, and  
**intestinal** transit in man)  
RN 79805-24-6 HCAPLUS  
CN  $\beta$ -Casomorphin (9CI) (CA INDEX NAME)  
  
\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*  
RN 98815-38-4 HCAPLUS  
CN L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:351796 HCAPLUS

DOCUMENT NUMBER: 122:157125

TITLE: Effect of bovine  $\beta$ -casomorphin-4-amide on **gastrointestinal** transit and pancreatic endocrine function in man

AUTHOR(S): Schulte-Frohlinde, E.; Schmid, R.; Brantl, V.; Schusdziarra, V.

CORPORATE SOURCE: Department Internal Medicine II, Technical University Munich, Munich, D-8000, Germany

SOURCE: [Beta]-Casomorphins Relat. Pept. [Int. Symp.], 2nd (1994), 155-60

CODEN: 60UMAA

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Opiates are well known therapeutic agents for the treatment of diarrhea and dysentery due to their potent inhibitory effects on **gastrointestinal** motility and secretion. In 8 healthy volunteers the effect of bovine  $\beta$ -casomorphin-4-amide ( $\beta$ -CM-4-NH<sub>2</sub>) was examined on mouth to cecum transit time by the H<sub>2</sub>-breath test. All overnight fasted subjects (age 20-29 yr) received either 250, 500 or 750 mg  $\beta$ -CM-4-NH<sub>2</sub>, or 4 mg loperamide dissolved in 100 mL water 5 min prior to ingestion of 50 g lactulose in 100 mL water. Transit time was delayed by at least 30 % with the 500 and 750 mg  $\beta$ -CM-4-NH<sub>2</sub> while 250 mg CM-4-NH<sub>2</sub> and 4 mg loperamide had no effect compared to control expts. There was no effect of  $\beta$ -CM-4-NH<sub>2</sub> on postprandial pancreatic endocrine function and carbohydrate metabolism. These data indicates that  $\beta$ -casomorphins might be of therapeutic usefulness in patients where prolongation of **gastrointestinal** transit is required, e.g. in patients suffering from diarrhea or short bowel syndrome.

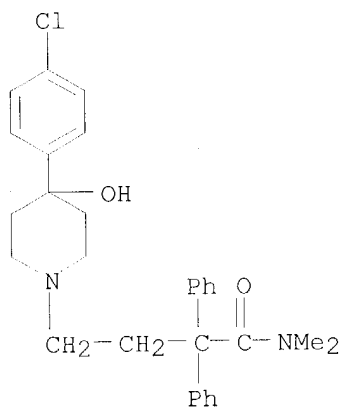
CC 13-6 (Mammalian Biochemistry)

ST casomorphin **gastrointestinal** transit pancreas endocrine function; antidiarrhea casomorphin; pancreatic hormone secretion casomorphin

IT Diarrhea (inhibitors;  $\beta$ -casomorphin-4-amide effect on **gastrointestinal** transit and pancreatic endocrine function in man in relation to diarrhea treatment)

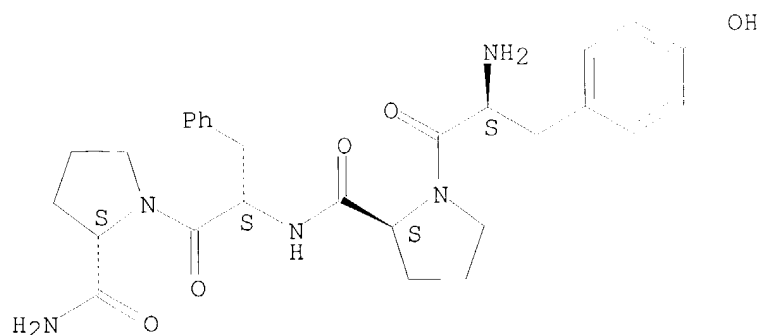
IT Blood sugar Digestive tract ( $\beta$ -casomorphin-4-amide effect on **gastrointestinal**

- transit and pancreatic endocrine function in man in relation to diarrhea treatment)
- IT Pancreatic hormones  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (β-casomorphin-4-amide effect on **gastrointestinal** transit and pancreatic endocrine function in man in relation to diarrhea treatment)
- IT 53179-11-6, Loperamide 74135-04-9, β-Casomorphin-4-amide  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (β-casomorphin-4-amide effect on **gastrointestinal** transit and pancreatic endocrine function in man in relation to diarrhea treatment)
- IT 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies 59763-91-6, Pancreatic polypeptide  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (β-casomorphin-4-amide effect on **gastrointestinal** transit and pancreatic endocrine function in man in relation to diarrhea treatment)
- IT 53179-11-6, Loperamide 74135-04-9, β-Casomorphin-4-amide  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (β-casomorphin-4-amide effect on **gastrointestinal** transit and pancreatic endocrine function in man in relation to diarrhea treatment)
- RN 53179-11-6 HCAPLUS  
 CN 1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl- (9CI) (CA INDEX NAME)



- RN 74135-04-9 HCAPLUS  
 CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 9004-10-8, Insulin, biological studies 9007-92-5,  
 Glucagon, biological studies 59763-91-6, Pancreatic polypeptide  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 ( $\beta$ -casomorphin-4-amide effect on **gastrointestinal**  
 transit and pancreatic endocrine function in man in relation to  
 diarrhea treatment)  
 RN 9004-10-8 HCAPLUS  
 CN Insulin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 9007-92-5 HCAPLUS  
 CN Glucagon (7CI, 8CI, 9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 59763-91-6 HCAPLUS  
 CN Pancreatic polypeptide (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

L28 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:351795 HCAPLUS

DOCUMENT NUMBER: 122:157124

TITLE: Effect of bovine  $\beta$ -casomorphin-4-amide on enteric  
 nerve pathways of the rat ileum

AUTHOR(S): Allescher, H. D.; Piller, C.; **Brantl, V.**;  
 Schusdziarra, V.

CORPORATE SOURCE: Department Internal Medicine II, Technical University  
 Munich, Munich, D-8000/80, Germany

SOURCE: [Beta]-Casomorphins Relat. Pept. [Int. Symp.], 2nd  
 (1994), 150-4  
 CODEN: 60UMAA

DOCUMENT TYPE: Conference

LANGUAGE: English

AB The ascending excitatory reflex is part of the myenteric reflex, which is  
 a major determinant of **intestinal** propulsion. The aim of the  
 study was to characterize the effect of casomorphin and its analog  
 casomorphin-4-amide on the ascending neural pathways in isolated segments  
 of rat ileum. The gut segments were incubated in an organ bath,  
 stimulated on the anal end by elec. field stimulation of the gut wall (20  
 V, 3pps. 2 ms) using platinum plates. The excitatory contractile response  
 was recorded manometrically 2 and 4 cm orally to the stimulation site.  
 The induced contractile response was inhibited via a naloxone-sensitive  
 mechanism by serosal application of casomorphin and casomorphin-4-amide.  
 However, the inhibition was less potent when compared to serosal

application of the selective kappa opioid agonist U-50,488. On the contrary, when the substances were applied intraluminally casomorphin and casomorphin-4-amide still decreased the induced contractile activity, but with this mode of application were more potent than the selective kappa opioid agonist U-50,488, which was almost inactive when applied intraluminally. These results demonstrate that casomorphins can inhibit **intestinal** motility from the serosal and the luminal side. The inhibitory effect when applied luminally could be due to a specific mode of action of casomorphins on the mucosa or mucosal nerve endings.

CC 13-6 (Mammalian Biochemistry)

ST beta casomorphin enteric nerve ileum

IT Opioids

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(endogenous,  $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum mediation by opioids)

IT Nerve

(enteric,  $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum)

IT **Intestine**

(ileum,  $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum)

IT Reflex

(peristaltic,  $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum)

IT **74135-04-9,  $\beta$ -Casomorphin-4-amide**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

( $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum)

IT **74135-04-9,  $\beta$ -Casomorphin-4-amide**

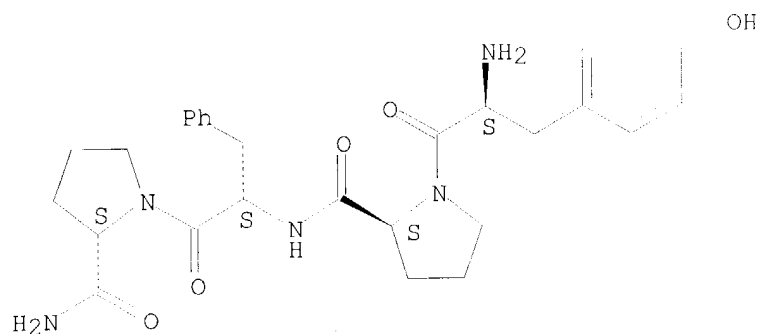
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

( $\beta$ -casomorphin-4-amide effect on enteric nerve pathways of ileum)

RN 74135-04-9 HCAPLUS

CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:351794 HCAPLUS

DOCUMENT NUMBER: 122:151663

TITLE:  $\beta$ -Casomorphins and **intestinal** net fluid transport in vivo

AUTHOR(S): Erll, G.; Hahn, A.; **Brantl, V.**; Daniel, H.

CORPORATE SOURCE: Institute Nutrition, Justus-Liebig-University,

SOURCE: Giessen, D-6300, Germany  
[Beta]-Casomorphins Relat. Pept. [Int. Symp.], 2nd  
(1994), 143-9  
CODEN: 60UMAA

DOCUMENT TYPE: Conference

LANGUAGE: English

AB The antisecretory activities of morphiceptin (bovine  $\beta$ -casomorphin-4-amide) and the synthetic  $\beta$ -casomorphin analog casokefamide (D-Ala<sup>2,4</sup>, Tyr<sup>5</sup>- $\beta$ -casomorphin-5-amide) were examined in vivo in ligated loops prepared from the proximal jejunum of rats. Net fluid secretion was induced by a heat-stable E.coli toxin in combination with theophylline. Luminal administration of morphiceptin revealed a significant antisecretory effect at relatively low concns. (10<sup>-7</sup> and 10<sup>-6</sup>M). In contrast, higher concns. (10<sup>-5</sup> - 10<sup>-2</sup>M) failed to alter fluid movement. Morphiceptin at a concentration of 10<sup>-6</sup> M was equally effective as a single dose of loperamide (4 mg/kg b.w.). When casokefamide was given into the **intestinal** lumen there was a significant reduction of fluid secretion at 10<sup>-3</sup> M but not at higher or lower concns., resp. Because coadministration of naloxone with the  $\beta$ -casomorphins caused a significant increase in fluid secretion rate as compared with controls the authors suggest that, besides opioid-specific antisecretory effects,  $\beta$ -casomorphins can addnl. elicit non-opioid secretory effects.

CC 2-5 (Mammalian Hormones)

ST beta casomorphin **intestine** fluid transport opioid; antidiarrhea morphiceptin casokefamide

IT Diarrhea  
(antidiarrheals; casokefamide and morphiceptin antidiarrheal activity)

IT Escherichia coli  
( $\beta$ -casomorphins effects on **intestinal** fluid transport induced by endotoxins)

IT **Intestine**  
( $\beta$ -casomorphins effects on **intestinal** fluid transport mediation by opioid and non-opioid mechanisms)

IT Toxins  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(endo-,  $\beta$ -casomorphins effects on **intestinal** fluid transport induced by endotoxins)

IT Opioids  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(endogenous,  $\beta$ -casomorphins effects on **intestinal** fluid transport mediation by opioid and non-opioid mechanisms)

IT **Intestine**  
(jejunum, proximal,  $\beta$ -casomorphins effects on **intestinal** fluid transport mediation by opioid and non-opioid mechanisms)

IT 74135-04-9, Morphiceptin 98815-38-4, Casokefamide  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(casokefamide and morphiceptin antidiarrheal activity)

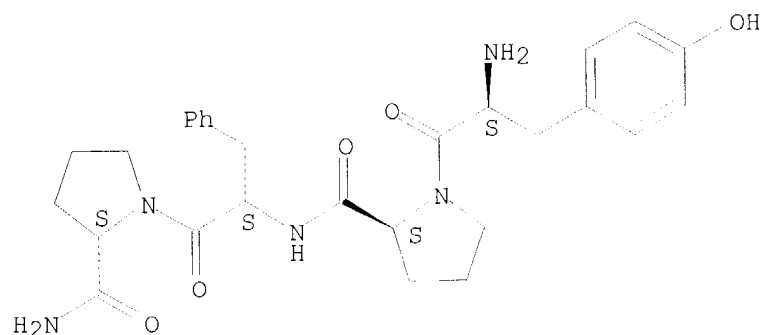
IT 74135-04-9, Morphiceptin 98815-38-4, Casokefamide  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(casokefamide and morphiceptin antidiarrheal activity)

RN 74135-04-9 HCAPLUS

CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

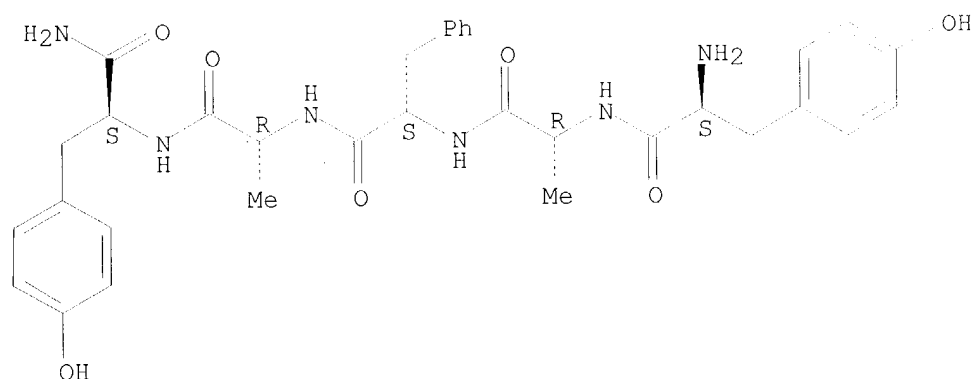




RN 98815-38-4 HCAPLUS

CN L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:805 HCAPLUS

DOCUMENT NUMBER: 114:805

TITLE: Absorption of  $\beta$ -casomorphins from autoperfusedlamb and piglet small **intestine**AUTHOR(S): Read, Leanna C.; Lord, Andrew P. D.; **Brantl,****Victor;** Koch, Gertrud

CORPORATE SOURCE: Waite Agric. Res. Inst., Univ. Adelaide, Glen Osmond, 5064, Australia

SOURCE: American Journal of Physiology (1990), 259(3, Pt. 1), G443-G452

CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

LANGUAGE: English

AB  $\beta$ -Casomorphins ( $\beta$ -CMs) derived from milk  $\beta$ -casein may exert various opiate activities in milk-fed infants. To assess the physiol. significance of  $\beta$ -CMs as a source of circulating opioids in infants, absorption rates of several  $\beta$ -CMs were determined under near-physiol. conditions using in situ autoperfused lamb **intestine**. The naturally occurring  $\beta$ -CMs,  $\beta$ -CM-7 and  $\beta$ -CM-4-amide, were absorbed readily into blood with no transfer into lymph. Uptake peaked within several minutes of the luminal infusion of peptide but then declined sharply and stopped within a further 10-15 min. The recovery in

blood, **intestinal** contents, and tissue at the end of the 30-min experiment was <1% of the infused dose. The low recovery was due to rapid proteolysis based on in vitro studies that demonstrated half-lives of <5 min in lamb blood, luminal contents, and lymph. The synthetic dipeptidyl peptidase IV-resistant analog  $\beta$ -[D-Ala<sup>2</sup>]CM-4-amide was stable during incubation in blood, lymph, or luminal contents and was absorbed into blood at rates that were maximal within several minutes and remained steady for the 30 min. Although natural  $\beta$ -CMs are transferred across the lamb small **intestine**, rapid degradation within the **intestinal** lumen, gut epithelium, and blood would prevent entry into the circulation under normal conditions. Val- $\beta$ -CM-7, a putative stable precursor, had similar stability and kinetics of absorption to  $\beta$ -CM-7, results that exclude Val- $\beta$ -CM-7 as a stable precursor for delivery of  $\beta$ -CMs to the circulation. Essentially identical results to those in lambs were obtained in 7-day-old piglets.

CC 2-5 (Mammalian Hormones)  
ST casomorphin **intestine** absorption newborn  
IT Newborn  
( $\beta$ -casomorphins absorption by small **intestine** of)

IT **Intestine**, metabolism  
(small,  $\beta$ -casomorphins absorption by, of newborn)

IT 72122-62-4 74135-04-9 79805-24-6D,  
 $\beta$ -Casomorphin, derivs. 83936-20-3 130968-81-9  
RL: PROC (Process)

(absorption of, by small **intestine** of newborn)  
IT 72122-62-4 74135-04-9 79805-24-6D,  
 $\beta$ -Casomorphin, derivs. 83936-20-3 130968-81-9  
RL: PROC (Process)

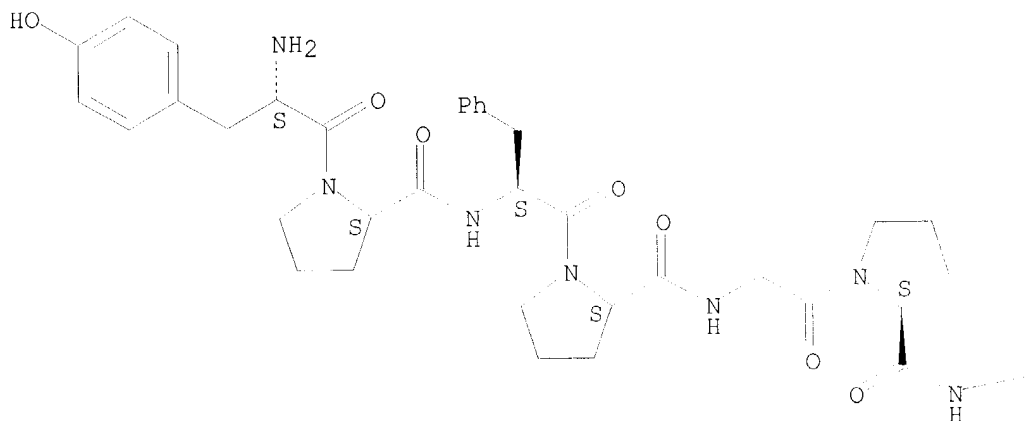
(absorption of, by small **intestine** of newborn)

RN 72122-62-4 HCAPLUS

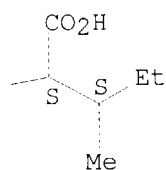
CN L-Isoleucine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolylglycyl-L-prolyl-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



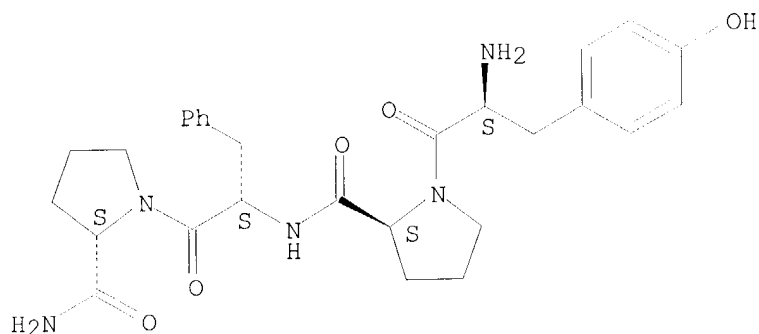
PAGE 1-B



RN 74135-04-9 HCAPLUS

CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79805-24-6 HCAPLUS

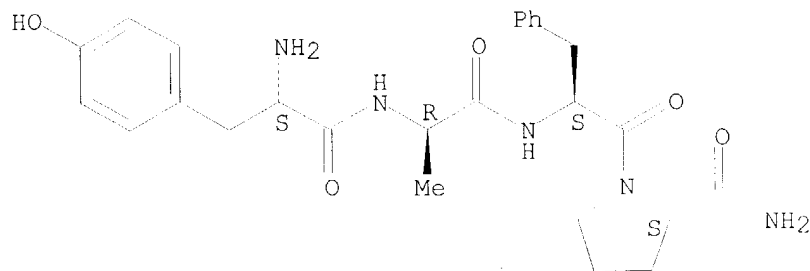
CN  $\beta$ -Casomorphin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 83936-20-3 HCAPLUS

CN L-Prolinamide, L-tyrosyl-D-alanyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

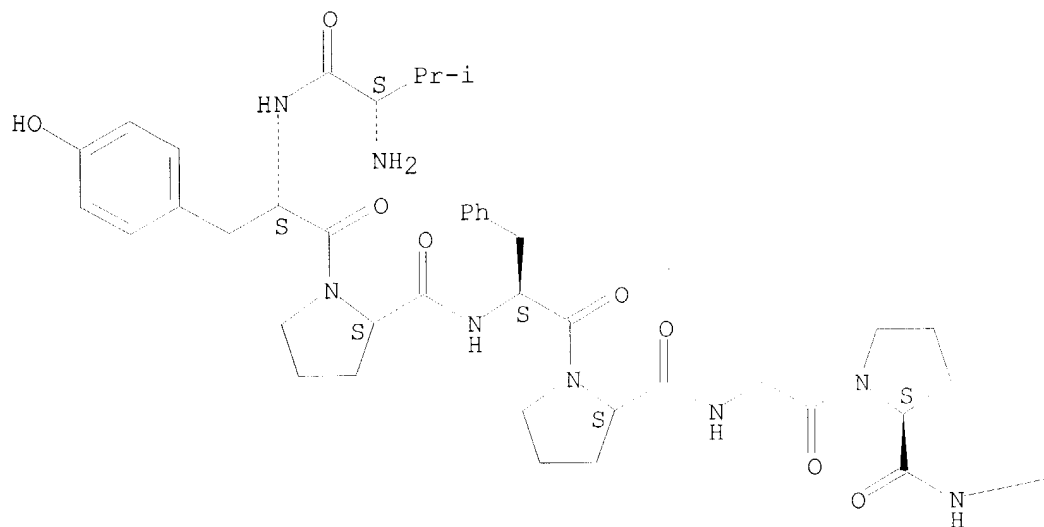


RN 130968-81-9 HCAPLUS

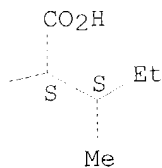
CN L-Isoleucine, L-valyl-L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolylglycyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L28 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1988:187282 HCAPLUS

DOCUMENT NUMBER: 108:187282  
 TITLE: Preparation of L-tyrosyl-L-prolyl-L-phenyl-L-alanyl-L-threonine and homologs as drugs  
 INVENTOR(S): Brantl, Victor  
 PATENT ASSIGNEE(S): Fed. Rep. Ger.  
 SOURCE: Ger. Offen., 23 pp.  
 CODEN: GWXXBX  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3514587	A1	19861030	DE 1985-3514587	19850423
EP 199331	A1	19861029	EP 1986-105507	19860421
EP 199331	B1	19890906		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
WO 8606381	A1	19861106	WO 1986-DE169	19860421
W: JP, US				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
EP 218650	A1	19870422	EP 1986-902336	19860421
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 62501422	T2	19870611	JP 1986-502293	19860421
AT 46173	E	19890915	AT 1986-105507	19860421
PRIORITY APPLN. INFO.: DE 1985-3514587 19850423				
EP 1986-105507 19860421				
WO 1986-DE169 19860421				
AB	H-Tyr-Pro-Phe-Thr-A-B-C-D-E-T [I; A, B, C, D, E = D-or L-amino acid residue, bond; T = OH, OR, NH, NHR, NR2, NHNHR2; R = C1-10 alkyl, adamantyl, cycloalkyl, aralkyl, Ph; R2 = H, C1-10 alkyl, cycloalkyl, aralkyl, (substituted) acyl, carbamoyl] were prepared as drugs with central nervous system, endocrine, immunomodulatory, metabolic, and antigenic activities. Thus, H-Tyr-Pro-Phe-Thr-OH (II) was prepd by the solution-phase method using benzyloxycarbonyl-protected amino acids as mixed anhydrides. II had an IC50 of 120.1 $\mu$ M in a test of inhibition of elec.-induced contraction of guinea pig <b>intestinal</b> tissue, vs. 0.1 $\mu$ M for normorphine.			
IC	ICM C07C007-06			
	ICS C07K005-10; A61K037-02; A61K037-18			
CC	34-3 (Amino Acids, Peptides, and Proteins)			
	Section cross-reference(s): 1			
ST	tyrosylprolylphenylalanylthreonine prepn drug; immunomodulator prepn peptide; central nervous system agent prepn peptide			
IT	Pharmaceuticals			
	(peptides)			
IT	Peptides, preparation			
	RL: SPN (Synthetic preparation); PREP (Preparation)			
	(preparation of tyrosylprolylphenylalanylthreonine and homologs as drugs)			
IT	Analgesics			
	Immunomodulators			
	Nervous system agents			
	(tyrosylprolylphenylalanylthreonine and homologs)			
IT	17350-17-3 18598-74-8 29713-96-0			
	RL: PROC (Process)			
	(conversion of, to mixed anhydride)			
IT	543-27-1			
	RL: PROC (Process)			
	(conversion of, to mixed anhydride with prolylphenylalanine derivative)			
IT	2577-46-0 19728-63-3 39994-75-7			

114102-50-0

RL: RCT (Reactant); RACT (Reactant or reagent)  
(peptide coupling of, in preparation of drug)

IT 114102-53-3P 114102-54-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation and deprotection of, in preparation of drug)

IT 97730-74-0P 97730-75-1P 114102-28-2P

114102-29-3P 114102-30-6P 114102-31-7P

114102-32-8P 114102-33-9P 114102-34-0P

114102-35-1P 114102-36-2P 114102-37-3P

114102-38-4P 114102-39-5P 114102-40-8P

114102-41-9P 114102-42-0P 114102-43-1P

114102-44-2P 114102-45-3P 114135-32-9P

114180-91-5P 114180-92-6P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
study); PREP (Preparation); USES (Uses)  
(preparation of, as drug)

IT 114102-46-4P 114102-47-5P 114102-48-6P

114102-49-7P 114102-51-1P 114102-52-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, as drug intermediate)

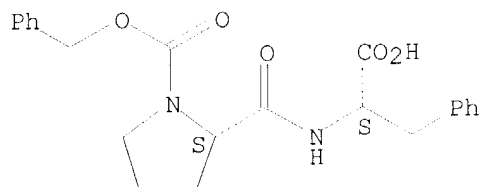
IT 17350-17-3 18598-74-8 29713-96-0

RL: PROC (Process)  
(conversion of, to mixed anhydride)

RN 17350-17-3 HCAPLUS

CN L-Phenylalanine, 1-[(phenylmethoxy)carbonyl]-L-prolyl- (9CI) (CA INDEX  
NAME)

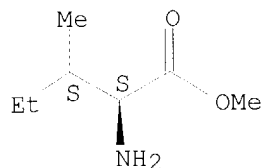
Absolute stereochemistry.



RN 18598-74-8 HCAPLUS

CN L-Isoleucine, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

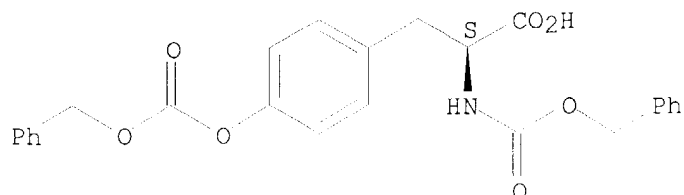


● HCl

RN 29713-96-0 HCAPLUS

CN L-Tyrosine, N-[(phenylmethoxy)carbonyl]-, phenylmethyl carbonate (ester)  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



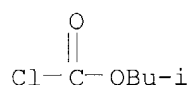
IT **543-27-1**

RL: PROC (Process)

(conversion of, to mixed anhydride with prolyphenylalanine derivative)

RN 543-27-1 HCAPLUS

CN Carbonochloridic acid, 2-methylpropyl ester (9CI) (CA INDEX NAME)



IT **2577-46-0 19728-63-3 39994-75-7**

**114102-50-0**

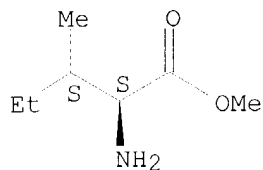
RL: RCT (Reactant); RACT (Reactant or reagent)

(peptide coupling of, in preparation of drug)

RN 2577-46-0 HCAPLUS

CN L-Isoleucine, methyl ester (9CI) (CA INDEX NAME)

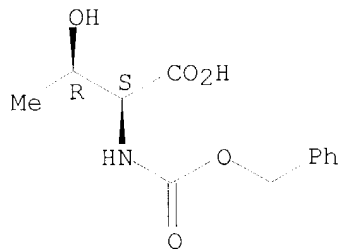
Absolute stereochemistry. Rotation (+).



RN 19728-63-3 HCAPLUS

CN L-Threonine, N-[(phenylmethoxy)carbonyl]- (9CI) (CA INDEX NAME)

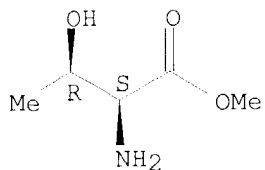
Absolute stereochemistry.



RN 39994-75-7 HCAPLUS

CN L-Threonine, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

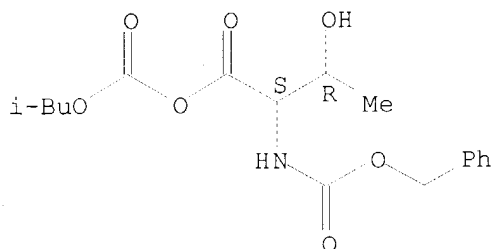


● HCl

RN 114102-50-0 HCAPLUS

CN L-Threonine, N-[(phenylmethoxy)carbonyl]-, anhydride with 2-methylpropyl hydrogen carbonate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



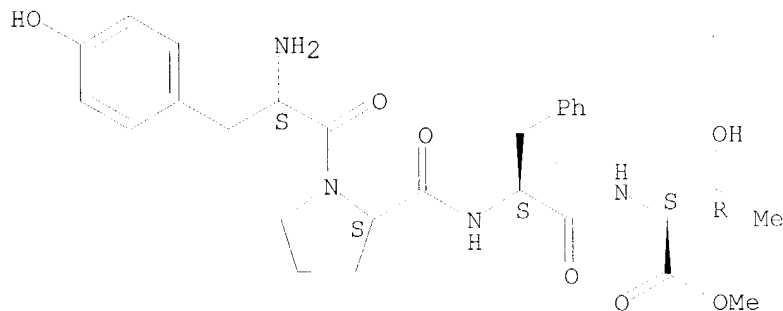
IT 114102-53-3P 114102-54-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and deprotection of, in preparation of drug)

RN 114102-53-3 HCAPLUS

CN L-Threonine, N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

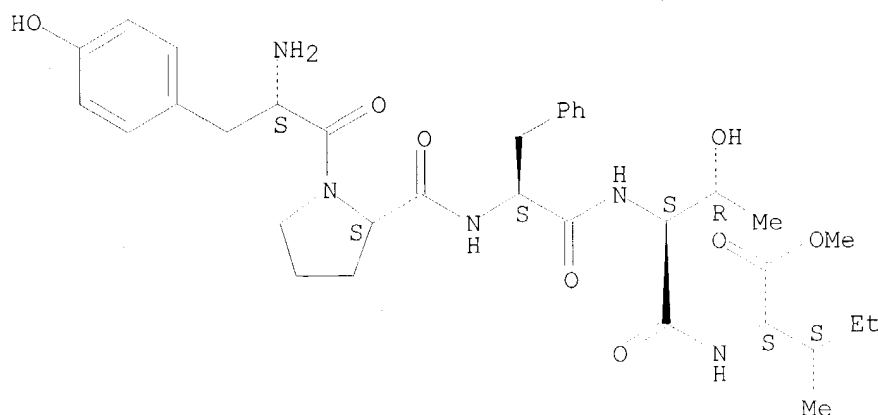


RN 114102-54-4 HCAPLUS

CN L-Isoleucine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.





IT 97730-74-0P 97730-75-1P 114102-28-2P  
114102-29-3P 114102-30-6P 114102-31-7P  
114102-32-8P 114102-33-9P 114102-34-0P  
114102-35-1P 114102-36-2P 114102-37-3P  
114102-38-4P 114102-39-5P 114102-40-8P  
114102-41-9P 114102-42-0P 114102-43-1P  
114102-44-2P 114102-45-3P 114135-32-9P  
114180-91-5P 114180-92-6P

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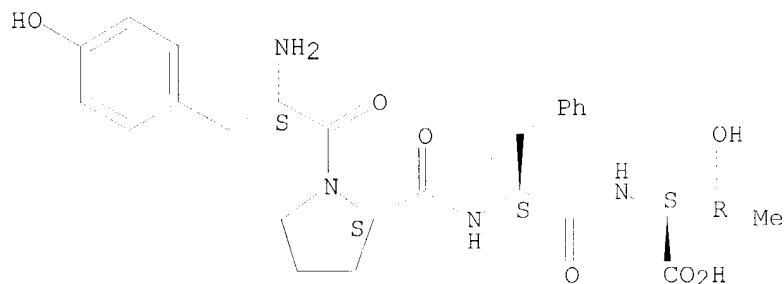
114180-91-SP 114180-92 SP
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)
      (preparation of, as drug)

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RN 97730-74-0 HCAPLUS

CN L-Threonine, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

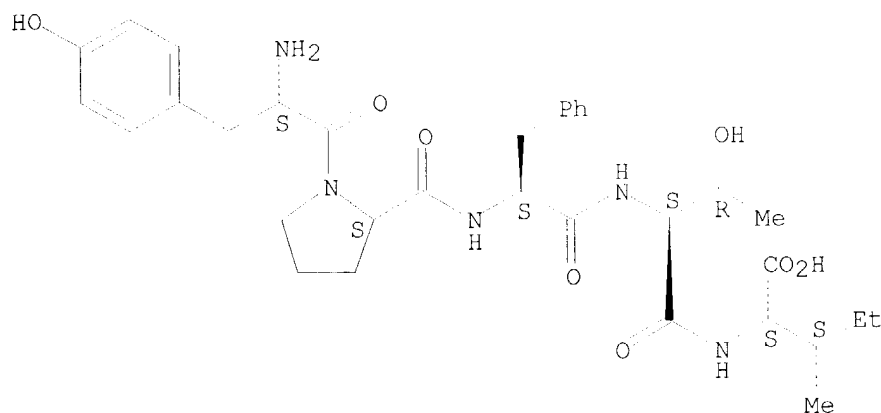
Absolute stereochemistry.



RN 97730-75-1 HCAPLUS

LN	37750 75 1	NON-203		
CN	L-Isoleucine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-threonyl- (9CI) (CA			
	INDEX NAME)			

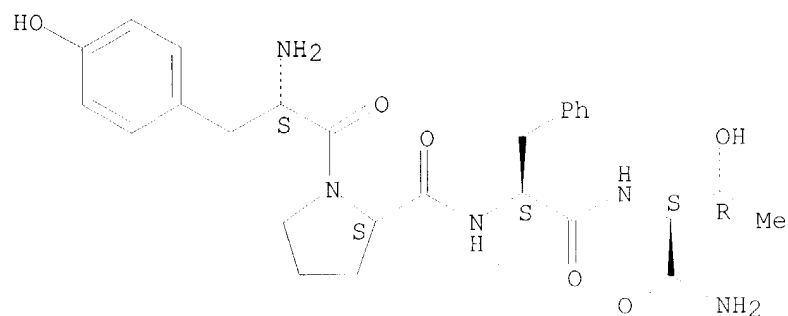
Absolute stereochemistry.



RN 114102-28-2 HCAPLUS

CN L-Threoninamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

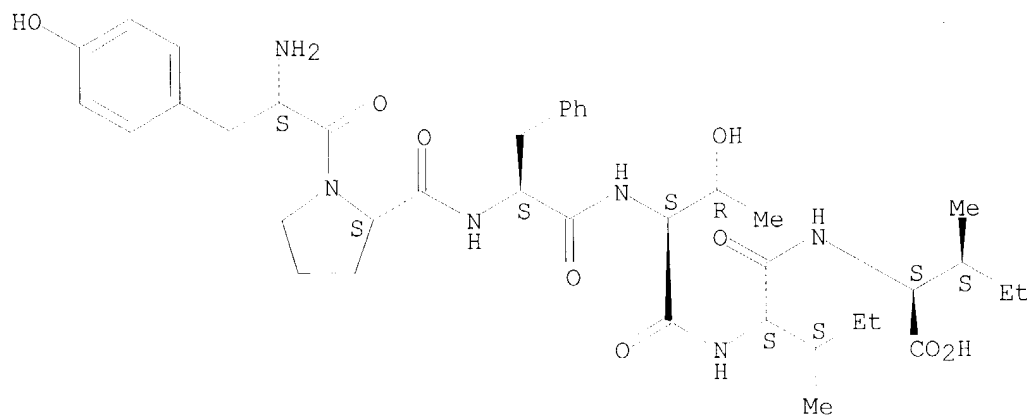
Absolute stereochemistry.



RN 114102-29-3 HCAPLUS

CN L-Isoleucine, N-[N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-L-isoleucyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

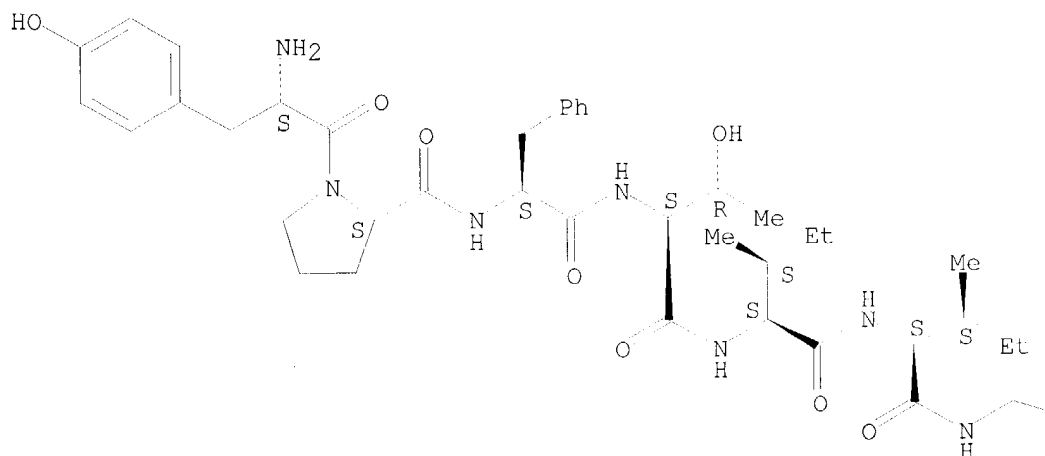


RN 114102-30-6 HCAPLUS

CN Glycine, N-[N-[N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-L-isoleucyl]-L-isoleucyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



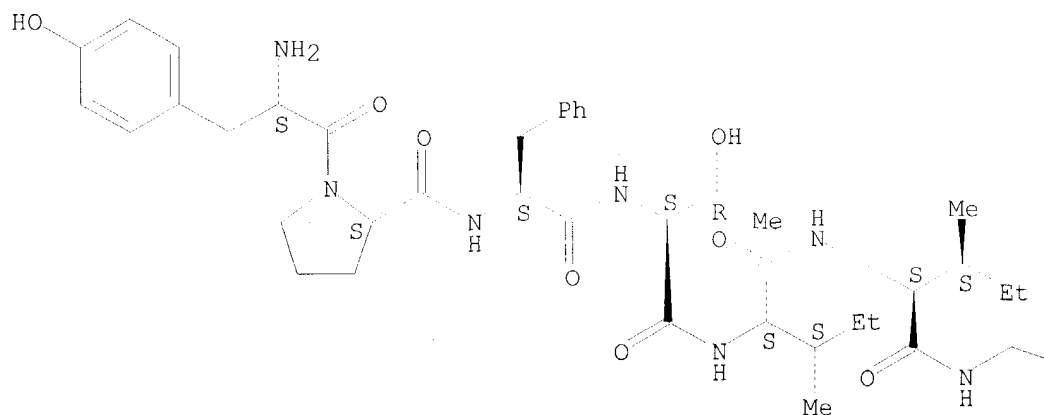
PAGE 1-B

CO<sub>2</sub>H

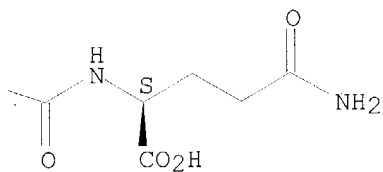
RN 114102-31-7 HCAPLUS  
 CN L-Glutamine, N2-[N-[N-[N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-L-isoleucyl]-L-isoleucyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

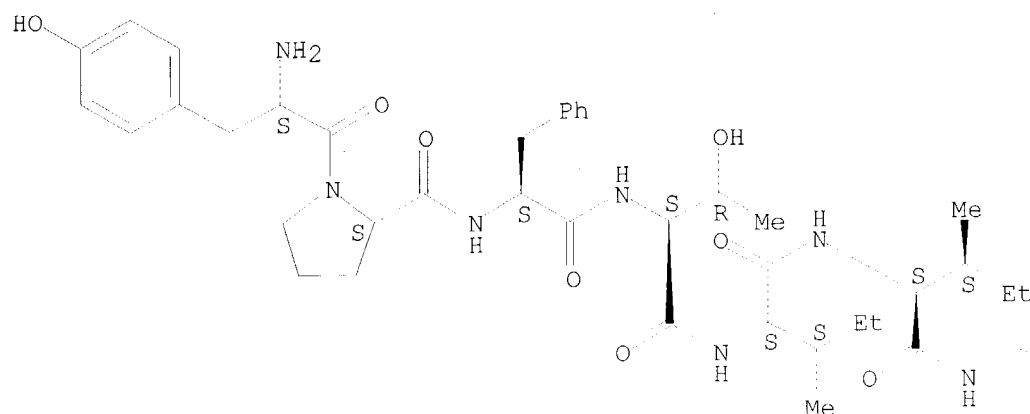


RN 114102-32-8 HCAPLUS

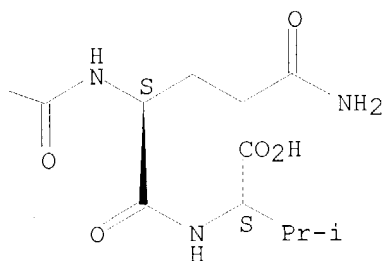
CN L-Valine, N-[N2-[N-[N-[N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-L-isoleucyl]-L-isoleucyl]glycyl]-L-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

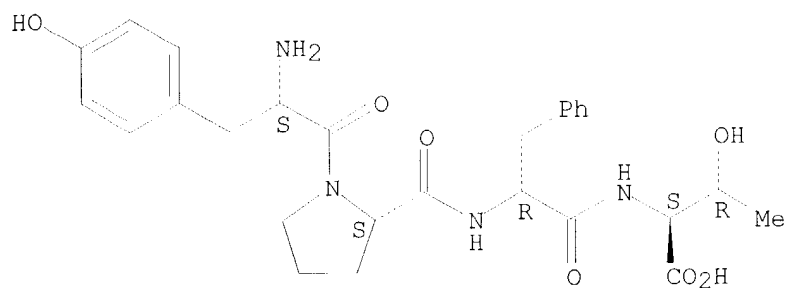


PAGE 1-B



RN 114102-33-9 HCAPLUS  
 CN L-Threonine, N-[N-(1-L-tyrosyl-L-prolyl)-D-phenylalanyl]- (9CI) (CA INDEX  
 NAME)

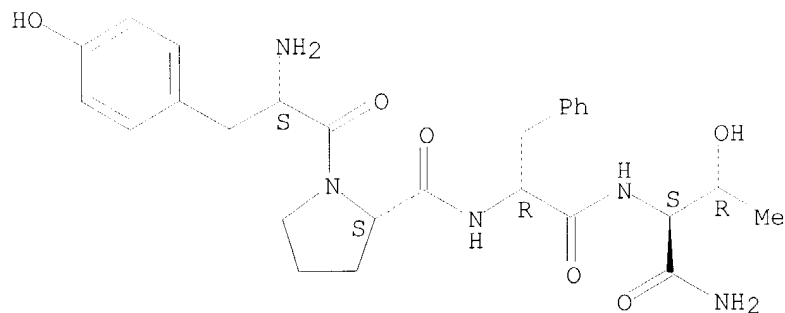
Absolute stereochemistry.



RN 114102-34-0 HCAPLUS

CN L-Threoninamide, L-tyrosyl-L-prolyl-D-phenylalanyl- (9CI) (CA INDEX NAME)

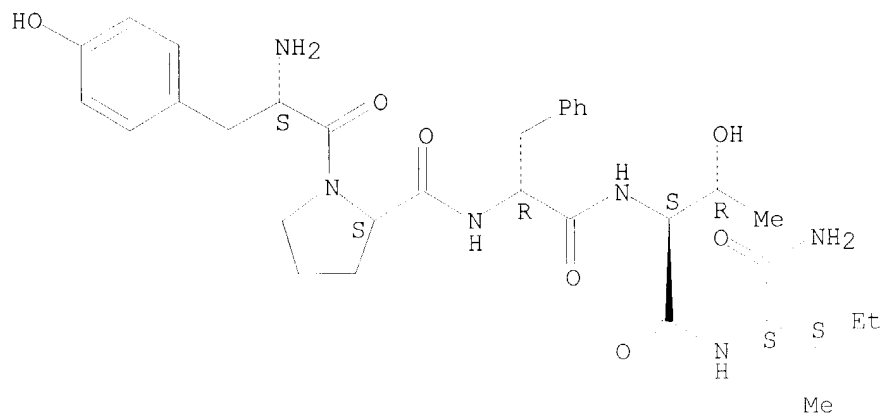
Absolute stereochemistry.



RN 114102-35-1 HCAPLUS

CN L-Isoleucinamide, L-tyrosyl-L-prolyl-D-phenylalanyl-L-threonyl- (9CI) (CA INDEX NAME)

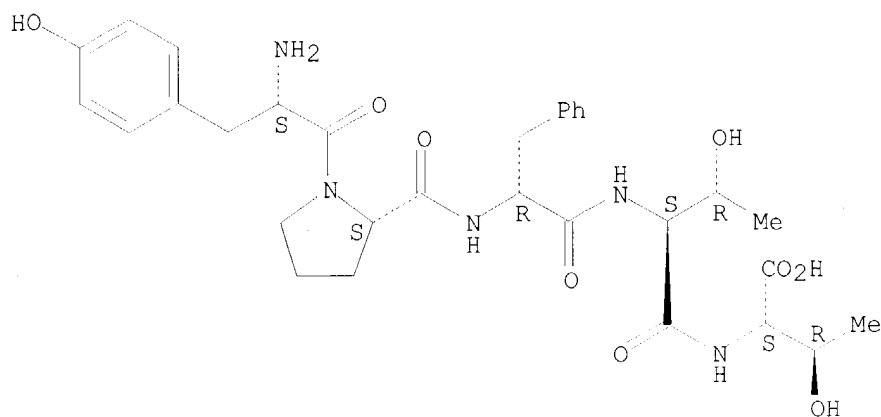
Absolute stereochemistry.



RN 114102-36-2 HCAPLUS

CN L-Threonine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-D-phenylalanyl]-L-threonyl]- (9CI) (CA INDEX NAME)

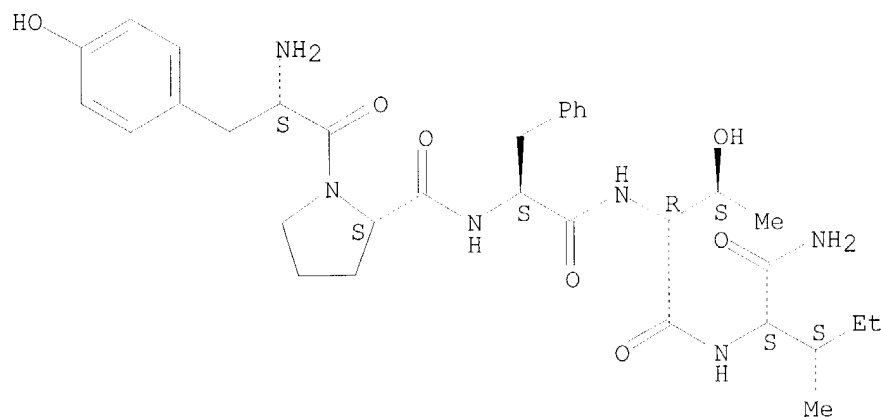
Absolute stereochemistry.



RN 114102-37-3 HCAPLUS

CN L-Isoleucinamide, L-tyrosyl-L-prolyl-L-phenylalanyl-D-threonyl- (9CI) (CA INDEX NAME)

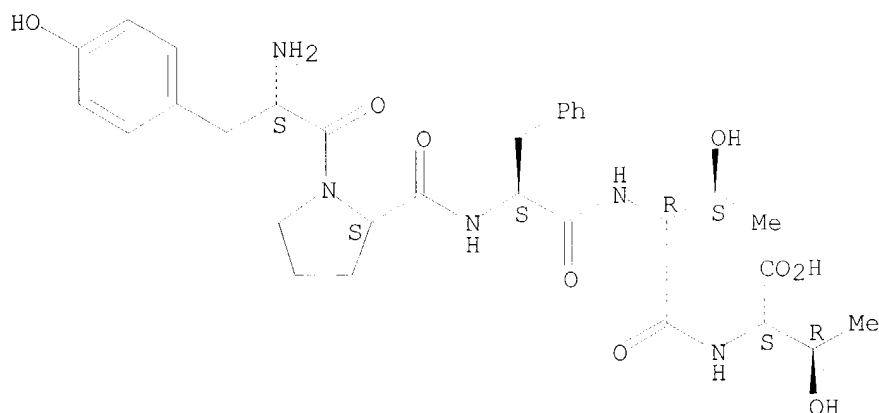
Absolute stereochemistry.



RN 114102-38-4 HCAPLUS

CN L-Threonine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-D-threonyl]- (9CI) (CA INDEX NAME)

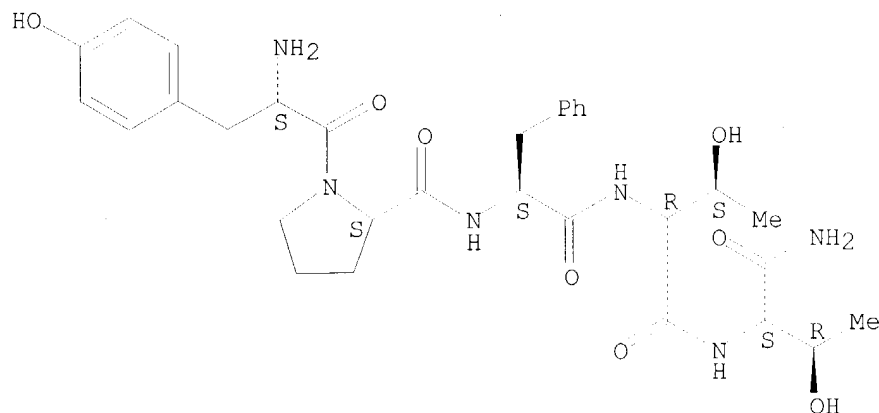
Absolute stereochemistry.



RN 114102-39-5 HCAPLUS

CN L-Threoninamide, L-tyrosyl-L-prolyl-L-phenylalanyl-D-threonyl- (9CI) (CA INDEX NAME)

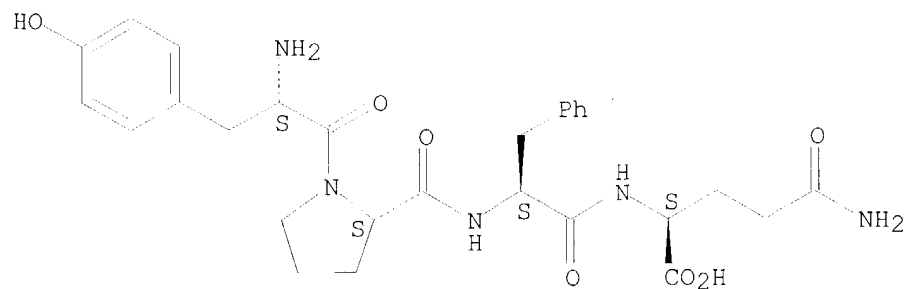
Absolute stereochemistry.



RN 114102-40-8 HCAPLUS

CN L-Glutamine, N2-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

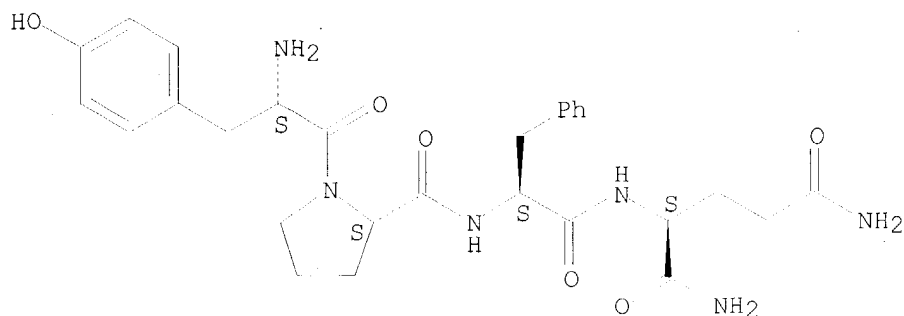


RN 114102-41-9 HCAPLUS



CN L-Glutamamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

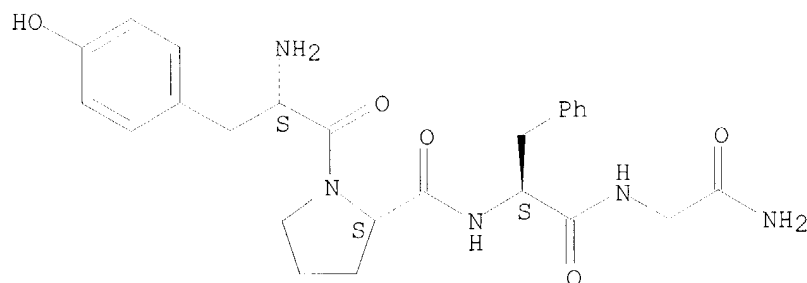
Absolute stereochemistry.



RN 114102-42-0 HCAPLUS

CN Glycinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

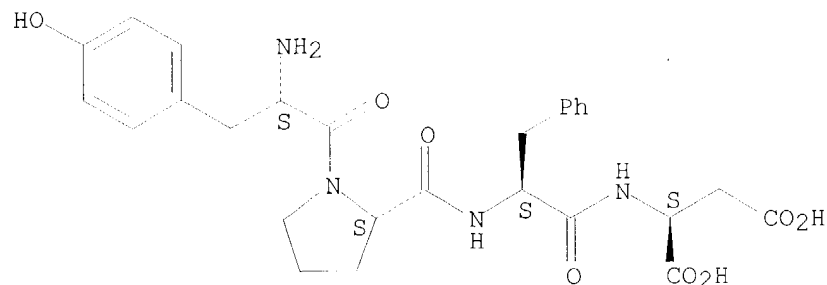
Absolute stereochemistry.



RN 114102-43-1 HCAPLUS

CN L-Aspartic acid, N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]- (9CI) (CA INDEX NAME)

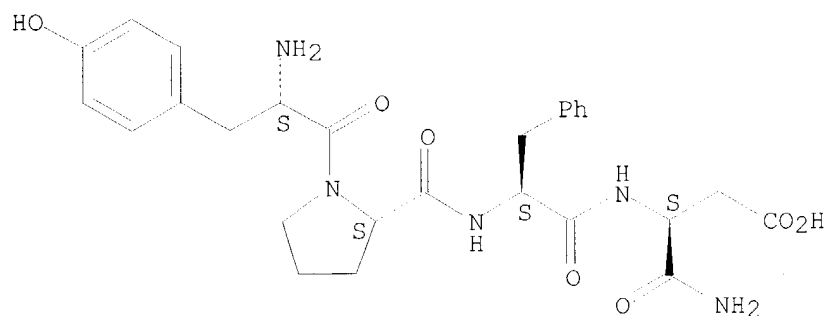
Absolute stereochemistry.



RN 114102-44-2 HCAPLUS

CN L-α-Asparagine, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

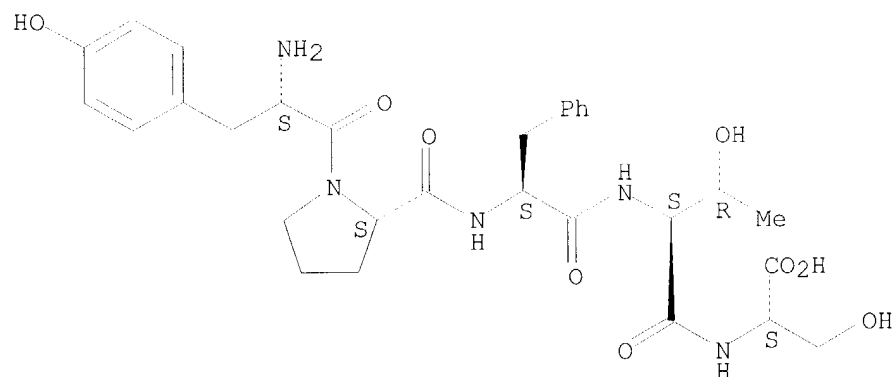
Absolute stereochemistry.



RN 114102-45-3 HCAPLUS

CN L-Serine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-  
(9CI) (CA INDEX NAME)

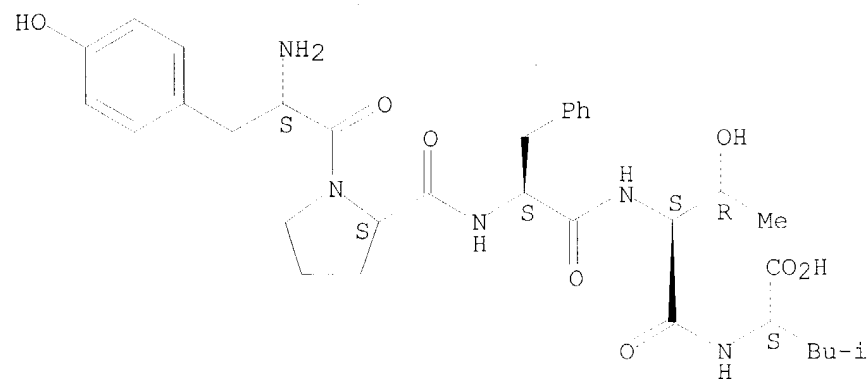
Absolute stereochemistry.



RN 114135-32-9 HCAPLUS

CN L-Leucine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

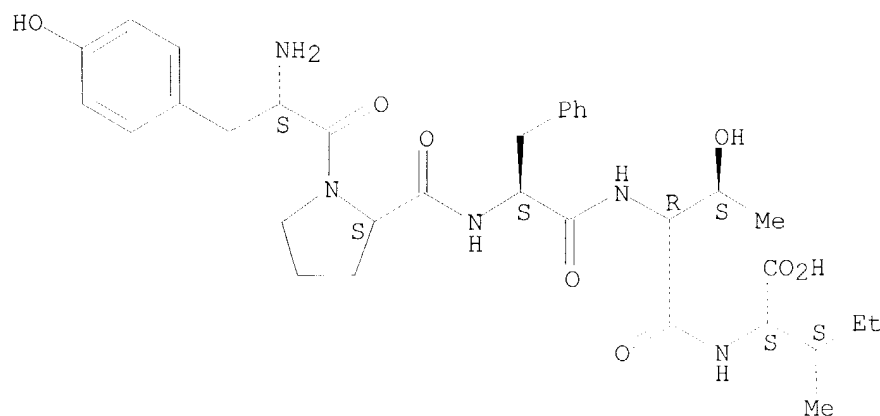


RN 114180-91-5 HCAPLUS

CN L-Isoleucine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-D-threonyl]-

(9CI) (CA INDEX NAME)

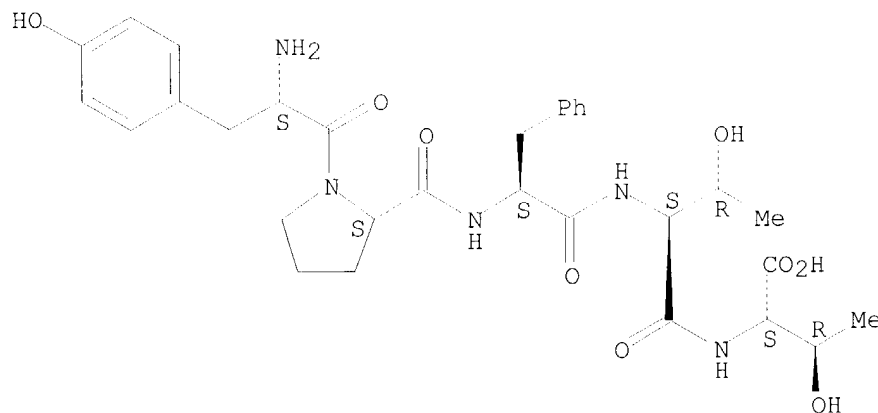
Absolute stereochemistry.



RN 114180-92-6 HCAPLUS

CN L-Threonine, N-[N-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-threonyl]-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 114102-46-4P 114102-47-5P 114102-48-6P

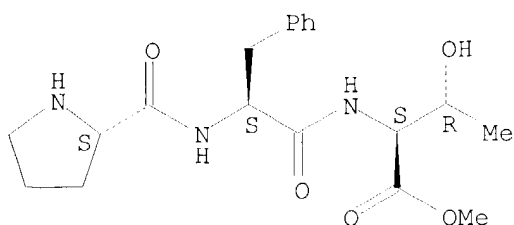
114102-49-7P 114102-51-1P 114102-52-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of, as drug intermediate)

RN 114102-46-4 HCAPLUS

CN L-Threonine, N-(N-L-prolyl-L-phenylalanyl)-, methyl ester (9CI) (CA INDEX  
NAME)

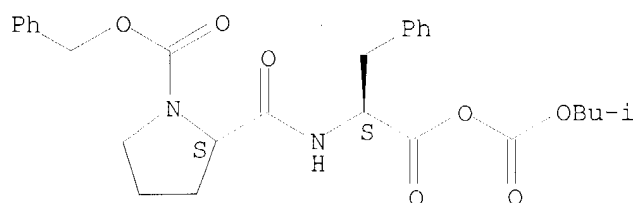
Absolute stereochemistry.



RN 114102-47-5 HCAPLUS

CN L-Phenylalanine, N-[1-[(phenylmethoxy)carbonyl]-L-prolyl]-, anhydride with 2-methylpropyl hydrogen carbonate (9CI) (CA INDEX NAME)

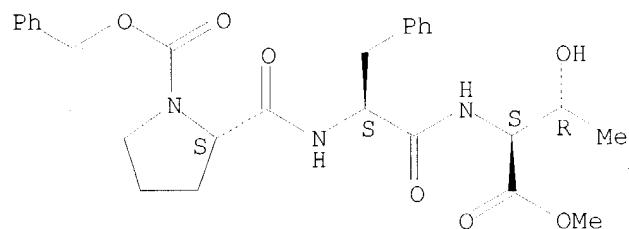
Absolute stereochemistry.



RN 114102-48-6 HCAPLUS

CN L-Threonine, N-[N-[1-[(phenylmethoxy)carbonyl]-L-prolyl]-L-phenylalanyl]-, methyl ester (9CI) (CA INDEX NAME)

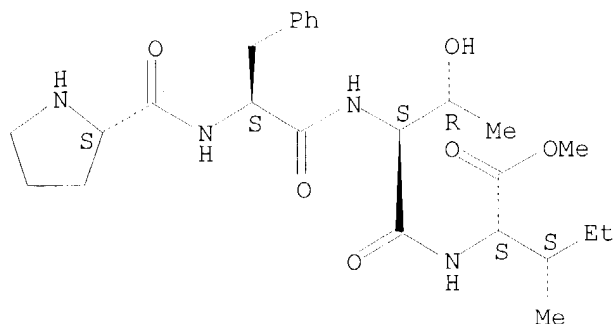
Absolute stereochemistry.



RN 114102-49-7 HCAPLUS

CN L-Isoleucine, N-[N-(N-L-prolyl-L-phenylalanyl)-L-threonyl]-, methyl ester (9CI) (CA INDEX NAME)

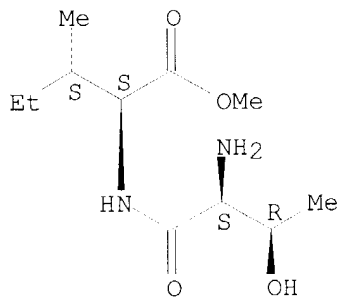
Absolute stereochemistry.



RN 114102-51-1 HCAPLUS

CN L-Isoleucine, N-L-threonyl-, methyl ester (9CI) (CA INDEX NAME)

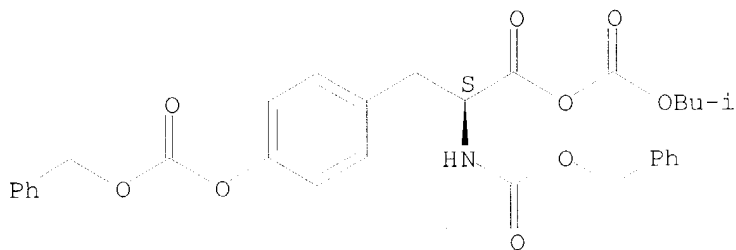
Absolute stereochemistry.



RN 114102-52-2 HCAPLUS

CN L-Tyrosine, N-[(phenylmethoxy)carbonyl]-, anhydride with 2-methylpropyl hydrogen carbonate, phenylmethyl carbonate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1988:75861 HCAPLUS

DOCUMENT NUMBER: 108:75861

TITLE: Preparation of tyrosylprolyltryptophanylthreonyl-containing peptides as drugs

INVENTOR(S): Brantl, Victor

PATENT ASSIGNEE(S): Fed. Rep. Ger.

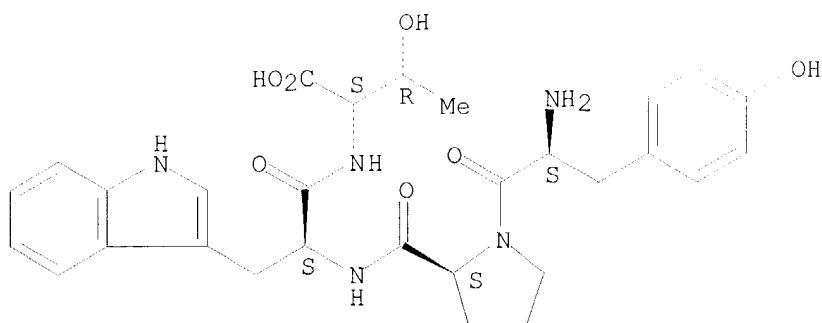
SOURCE: Ger. Offen., 5 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3618407	A1	19871203	DE 1986-3618407	19860531
EP 248231	A2	19871209	EP 1987-106649	19870507
EP 248231	A3	19900509		
EP 248231	B1	19930728		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 92078	E	19930815	AT 1987-106649	19870507
JP 62286997	A2	19871212	JP 1987-112229	19870508
PRIORITY APPLN. INFO.:				
			DE 1986-3618407	19860531
			EP 1987-106649	19870507
AB	H-Tyr-Pro-Trp-Thr-X-T (I; T = OH, OR, NH <sub>2</sub> , NHR, NR <sub>2</sub> , NHNHR <sub>2</sub> ; R = substituted alkyl, adamantyl, cycloalkyl, Ph, aralkyl; R <sub>2</sub> = H, alkyl, cycloalkyl, aralkyl, acyl, alkylcarbonyl; X = 0-6 D-ro L-amino acid residues) and their pharmaceutically acceptable salts were prepared as drugs. H-Tyr-Pro-Trp-Thr-OH (II) was prepared by the solid phase method using Fmoc-protected amino acids. II inhibited elec.-induced contractions of guinea pig <b>intestine</b> with an IC <sub>50</sub> of 45.2 µM, vs. 0.1 µM for normorphine.			
IC	ICM C07K007-06			
	ICS A61K037-02; G01N033-68			
ICA	C07K015-06			
CC	34-3 (Amino Acids, Peptides, and Proteins)			
	Section cross-reference(s): 1			
ST	peptide prepn drug; tyrosylprolyltryptophanylthreonyl contg peptide prepn drug; analgesic tyrosylprolyltryptophanylthreonyl contg peptide; tranquilizer tyrosylprolyltryptophanylthreonyl contg peptide			
IT	Analgesics			
	(tyrosylprolyltryptophanylthreonine containing peptides)			
IT	103930-64-9P 103930-65-0P 112747-34-9P 112747-35-0P 112747-36-1P 112747-37-2P 112747-38-3P 112747-39-4P 112747-40-7P 112747-41-8P 112747-42-9P 112747-43-0P 112747-44-1P 112747-45-2P 112765-57-8P 112765-58-9P			
	RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of, as drug)			
IT	103930-64-9P 103930-65-0P 112747-34-9P 112747-35-0P 112747-36-1P 112747-37-2P 112747-38-3P 112747-39-4P 112747-40-7P 112747-41-8P 112747-42-9P 112747-43-0P 112747-44-1P 112747-45-2P 112765-57-8P 112765-58-9P			
	RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of, as drug)			
RN	103930-64-9 HCAPLUS			
CN	L-Threonine, L-tyrosyl-L-prolyl-L-tryptophyl- (9CI) (CA INDEX NAME)			

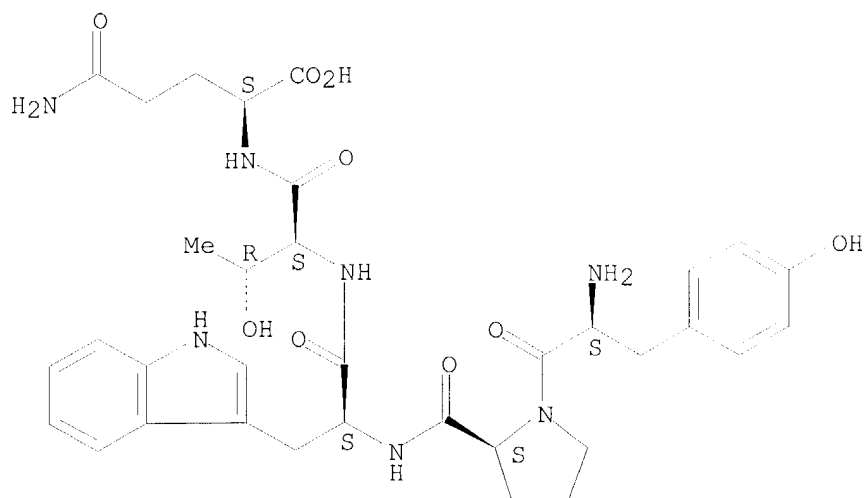
Absolute stereochemistry.



RN 103930-65-0 HCAPLUS

CN L-Glutamine, L-tyrosyl-L-prolyl-L-tryptophyl-L-threonyl- (9CI) (CA INDEX NAME)

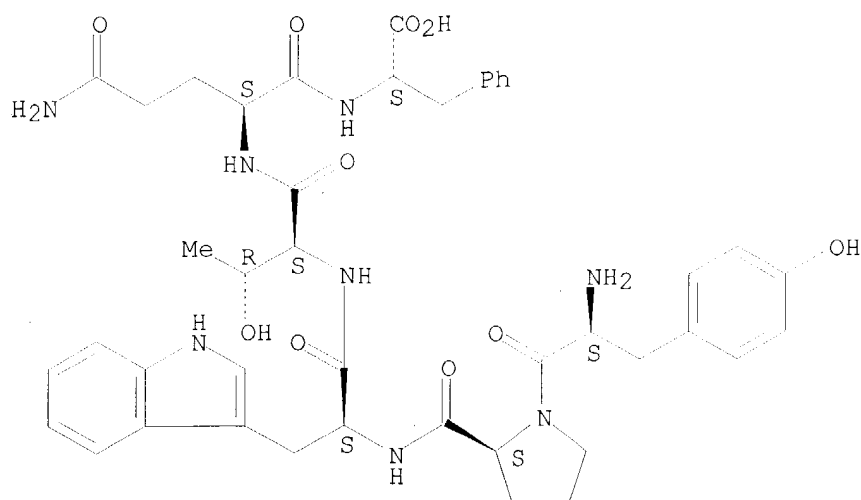
Absolute stereochemistry.



RN 112747-34-9 HCAPLUS

CN L-Phenylalanine, N-[N2-[N-[N-(1-L-tyrosyl-L-prolyl)-L-tryptophyl]-L-threonyl]-L-glutaminyl]- (9CI) (CA INDEX NAME)

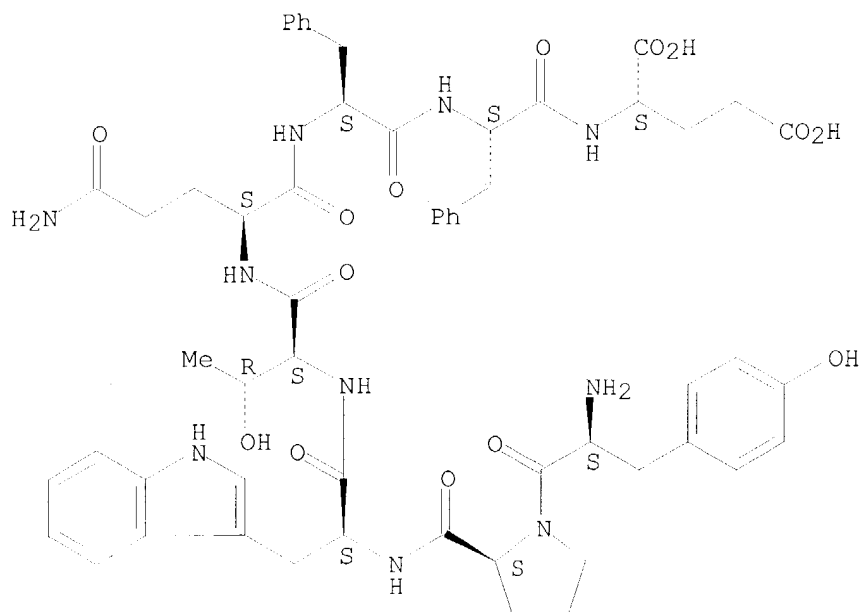
Absolute stereochemistry.



RN 112747-35-0 HCAPLUS

CN L-Glutamic acid, N-[N-[N-[N2-[N-[N-(1-L-tyrosyl-L-prolyl)-L-tryptophyl]-L-threonyl]-L-glutaminy]-L-phenylalanyl]-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



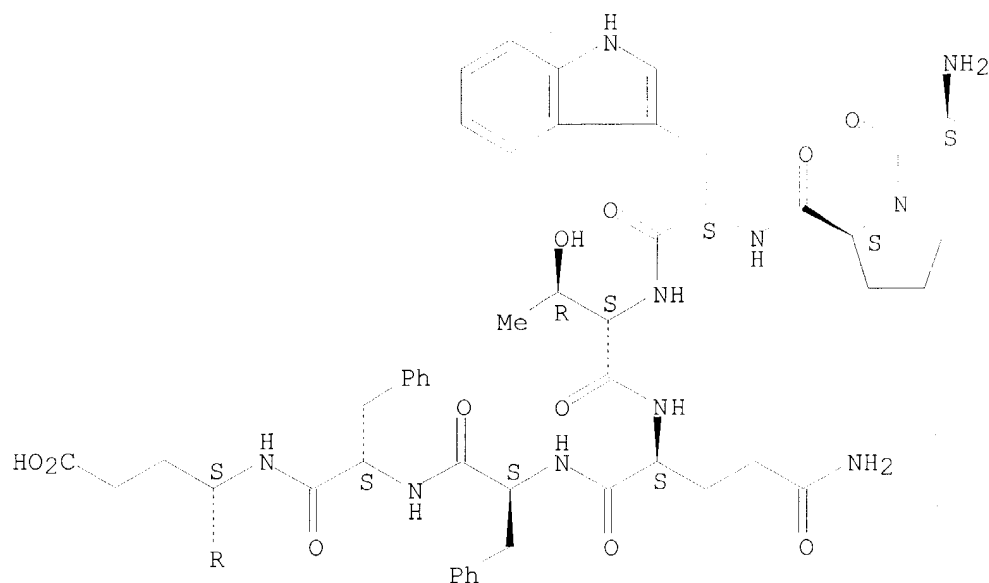
RN 112747-36-1 HCAPLUS

CN L-Aspartic acid, N-[N-[N-[N-[N2-[N-[N-(1-L-tyrosyl-L-prolyl)-L-tryptophyl]-L-threonyl]-L-glutaminy]-L-phenylalanyl]-L-phenylalanyl]-L-α-glutamyl]- (9CI) (CA INDEX NAME)

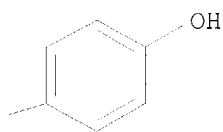
Absolute stereochemistry.



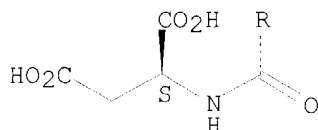
PAGE 1-A



PAGE 1-B



PAGE 2-A

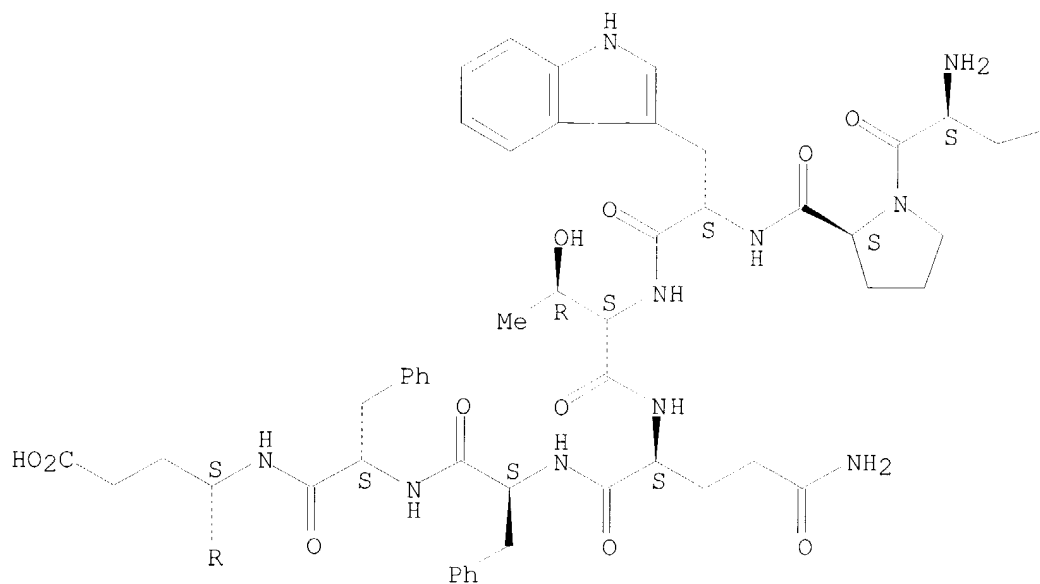


RN 112747-37-2 HCAPLUS

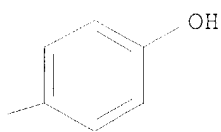
CN L-Serine, N-[N-[N-[N-[N2-[N-[N-(1-L-tyrosyl-L-prolyl)-L-tryptophyl]-L-threonyl]-L-glutaminy]-L-phenylalanyl]-L-phenylalanyl]-L-α-glutamyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

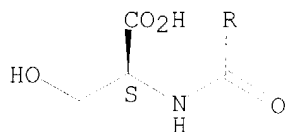
PAGE 1-A



PAGE 1-B



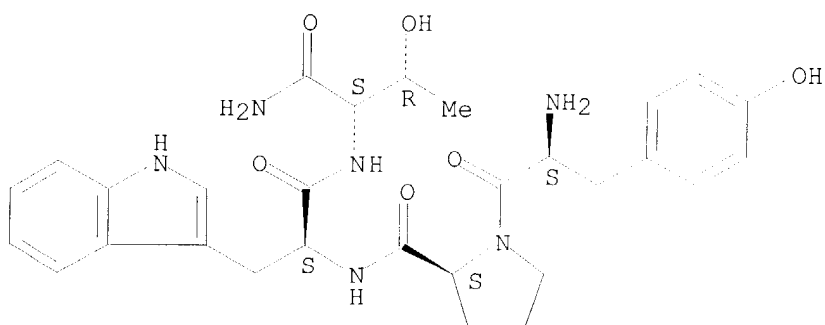
PAGE 2-A



RN 112747-38-3 HCAPLUS

CN L-Threoninamide, L-tyrosyl-L-prolyl-L-tryptophyl- (9CI) (CA INDEX NAME)

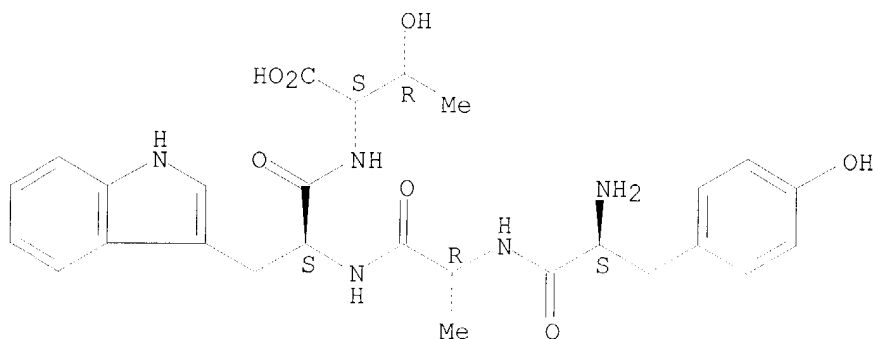
Absolute stereochemistry.



RN 112747-39-4 HCAPLUS

CN L-Threonine, N-[N-(N-L-tyrosyl-D-alanyl)-L-tryptophyl]- (9CI) (CA INDEX NAME)

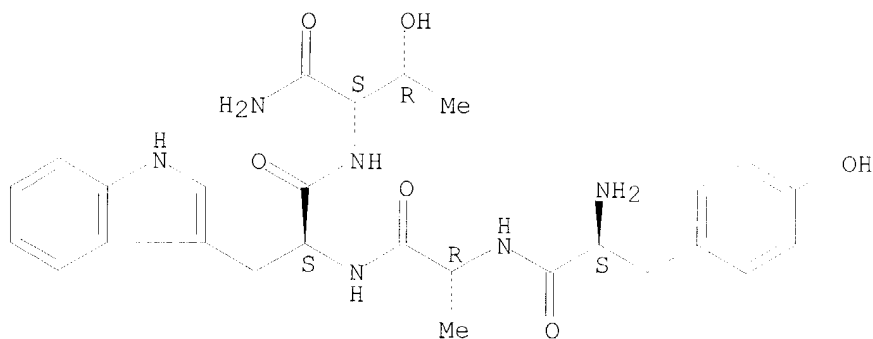
Absolute stereochemistry.



RN 112747-40-7 HCAPLUS

CN L-Threoninamide, L-tyrosyl-D-alanyl-L-tryptophyl- (9CI) (CA INDEX NAME)

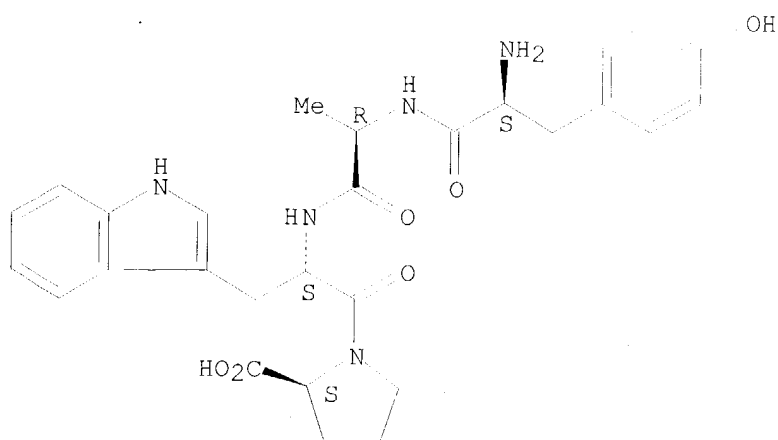
Absolute stereochemistry.



RN 112747-41-8 HCAPLUS

CN L-Proline, 1-[N-(N-L-tyrosyl-D-alanyl)-L-tryptophyl]- (9CI) (CA INDEX NAME)

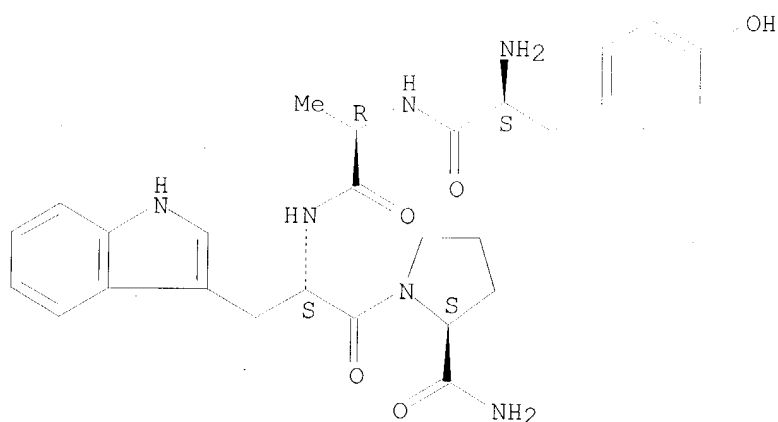
Absolute stereochemistry.



RN 112747-42-9 HCAPLUS

CN L-Prolinamide, L-tyrosyl-D-alanyl-L-tryptophyl- (9CI) (CA INDEX NAME)

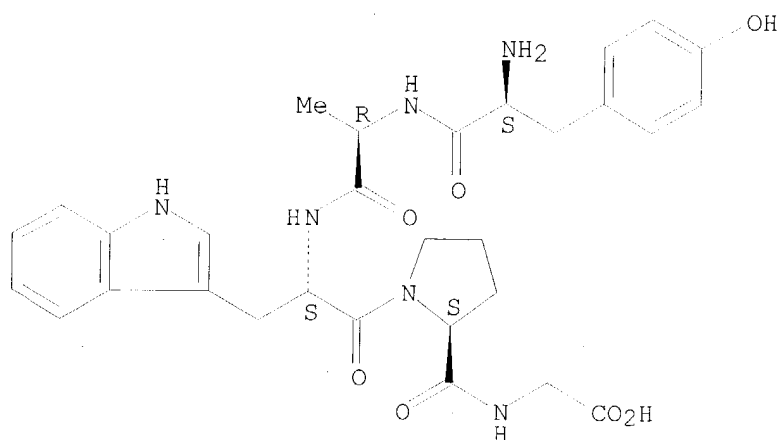
Absolute stereochemistry.



RN 112747-43-0 HCAPLUS

CN Glycine, N-[1-[N-(N-L-tyrosyl-D-alanyl)-L-tryptophyl]-L-prolyl]- (9CI)  
(CA INDEX NAME)

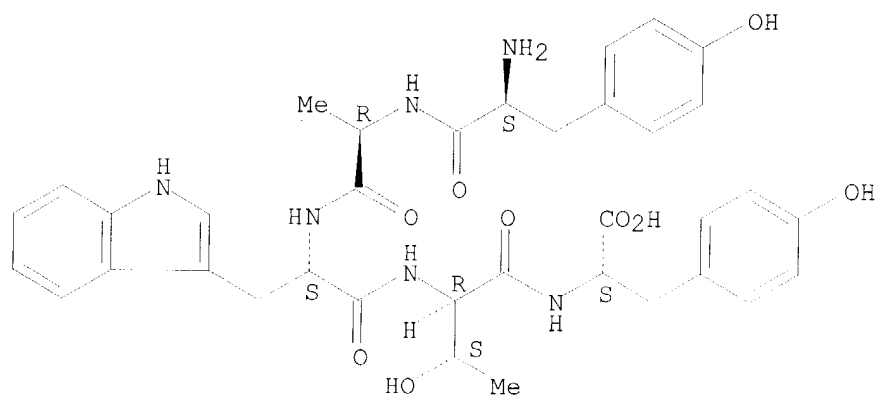
Absolute stereochemistry.



RN 112747-44-1 HCAPLUS

CN L-Tyrosine, N-[N-[N-(N-L-tyrosyl-D-alanyl)-L-tryptophyl]-D-threonyl]-  
(9CI) (CA INDEX NAME)

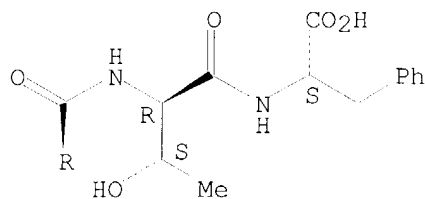
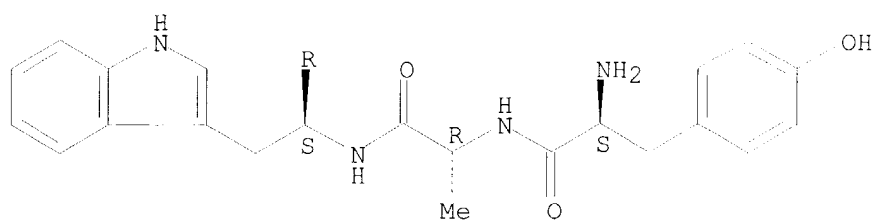
Absolute stereochemistry.



RN 112747-45-2 HCAPLUS

CN L-Phenylalanine, N-[N-[N-(N-L-tyrosyl-D-alanyl)-L-tryptophyl]-D-threonyl]-  
(9CI) (CA INDEX NAME)

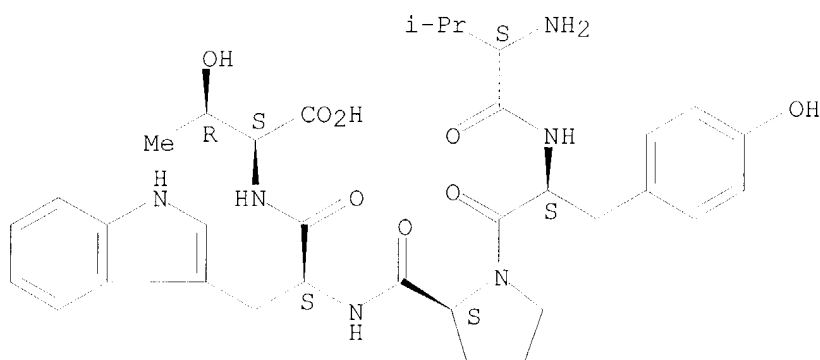
Absolute stereochemistry.



RN 112765-57-8 HCAPLUS

CN L-Threonine, L-valyl-L-tyrosyl-L-prolyl-L-tryptophyl- (9CI) (CA INDEX NAME)

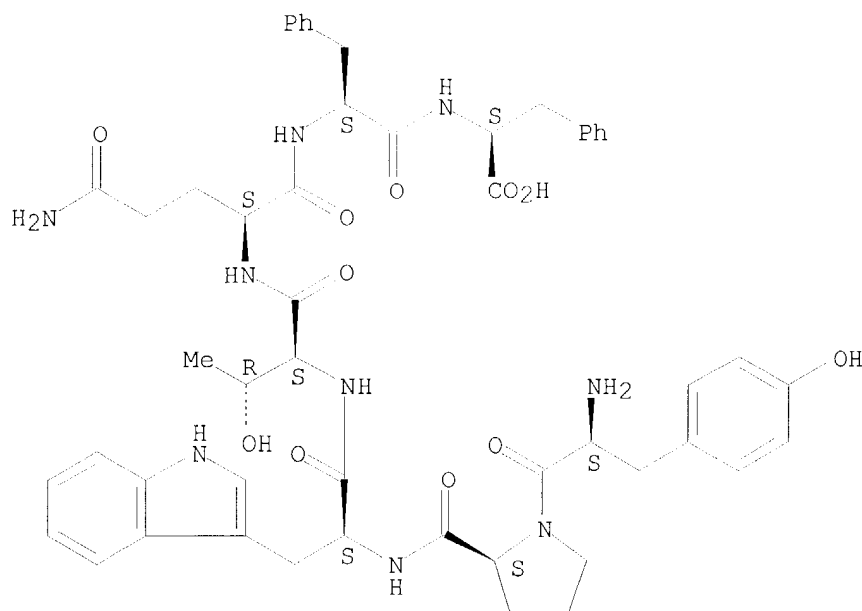
Absolute stereochemistry.



RN 112765-58-9 HCAPLUS

CN L-Phenylalanine, N-[N-[N2-[N-[N-(1-L-tyrosyl-L-prolyl)-L-tryptophyl]-L-threonyl]-L-glutamyl]-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1986:128613 HCAPLUS

DOCUMENT NUMBER: 104:128613

TITLE: In vitro effects of  $\beta$ -casomorphins on ion transport in rabbit ileum

AUTHOR(S): Hautefeuille, Matthieu; Brantl, Victor; Dumontier, Anne Marie; Desjeux, Jehan Francois

CORPORATE SOURCE: Unite Rech. Diabete Nutr. Chez Enfant, Inst. Natl. Sante Rech. Med., Paris, 75010, Fr.

SOURCE: American Journal of Physiology (1986), 250(1, Pt. 1), G92-G97

CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of natural  $\beta$ -casomorphin-4-OH (Tyr-Pro-Phe-Pro-OH) ( $\beta$ -CM-4-OH) [74171-19-0],  $\beta$ -CM-5-OH (Tyr-Pro-Phe-Pro-Gly-OH) [72122-63-5], and 3 related analogs on electrolyte transport were examined in rabbit ileum in vitro. At concns. of  $10^{-7}$ - $10^{-3}$  M, the 3 analogs  $\beta$ -[D-Ala<sup>2</sup>]CM-4-NH<sub>2</sub> [83936-20-3],  $\beta$ -[D-Ala<sup>2</sup>,Met<sup>5</sup>]CM-5-NH<sub>2</sub> [83936-23-6], and  $\beta$ -[D-Ala<sup>2</sup>,4,Tyr<sup>5</sup>]CM-5-NH<sub>2</sub> [100817-40-1], caused a dose-dependent, naloxone-reversible reduction in short-circuit current (Isc) after addition to the serosal side of the preparation  $\beta$ -[D-Ala<sup>2</sup>,4,Tyr<sup>5</sup>]CM-5-NH<sub>2</sub> also decreased Isc after mucosal addition. Serosal addition of the same analog stimulated absorption of Na<sup>+</sup> and Cl<sup>-</sup> (+2.90 and +2.12  $\mu$ equivalent/h/cm<sup>2</sup>, resp.) and inhibited residual flux (-1.80). The natural  $\beta$ -casomorphins tested did not decrease Isc. Thus,  $\beta$ -casomorphin analogs stimulate **intestinal** absorption of electrolytes by an opioid mechanism. The fact that  $\beta$ -[D-Ala<sup>2</sup>,4,Tyr<sup>5</sup>]CM-5-NH<sub>2</sub> was effective on the mucosal side favors the hypothesis that certain food-related opioid peptides might be absorbed by the **intestine**.

CC 17-13 (Food and Feed Chemistry)

ST casomorphin electrolyte absorption **intestine**

IT Electrolytes

(absorption of, by **intestine**,  $\beta$ -casomorphins stimulation of)

IT Receptors  
RL: BIOL (Biological study)  
(for opioids,  $\beta$ -casomorphin stimulation of electrolyte absorption by **intestine** mediation by)

IT **Intestine**, metabolism  
(ileum, electrolyte absorption by,  $\beta$ -casomorphins stimulation of, opioid mechanism of)

IT **7440-23-5**, biological studies **16887-00-6**, biological studies  
RL: BIOL (Biological study)  
(absorption of, by **intestine**,  $\beta$ -casomorphins stimulation of)

IT **72122-63-5 74171-19-0 79805-24-6D**, analogs  
**83936-20-3 83936-23-6 100817-40-1**  
RL: BIOL (Biological study)  
(electrolyte absorption by **intestine** stimulation by, opioid mechanism of)

IT **7440-23-5**, biological studies **16887-00-6**, biological studies  
RL: BIOL (Biological study)  
(absorption of, by **intestine**,  $\beta$ -casomorphins stimulation of)

RN 7440-23-5 HCAPLUS  
CN Sodium (8CI, 9CI) (CA INDEX NAME)

Na

RN 16887-00-6 HCAPLUS  
CN Chloride (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

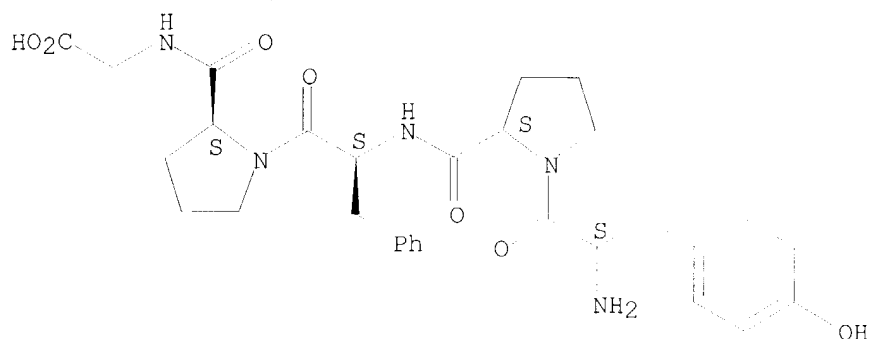
Cl<sup>-</sup>

IT **72122-63-5 74171-19-0 79805-24-6D**, analogs  
**83936-20-3 83936-23-6 100817-40-1**  
RL: BIOL (Biological study)  
(electrolyte absorption by **intestine** stimulation by, opioid mechanism of)

RN 72122-63-5 HCAPLUS  
CN Glycine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

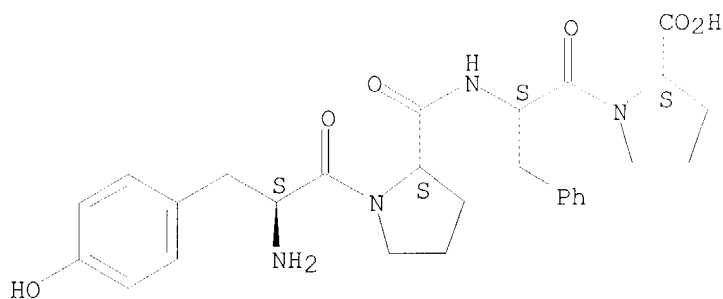




RN 74171-19-0 HCAPLUS

CN L-Proline, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79805-24-6 HCAPLUS

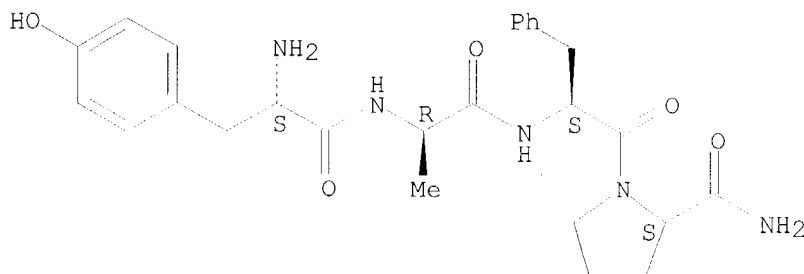
CN  $\beta$ -Casomorphin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 83936-20-3 HCAPLUS

CN L-Prolinamide, L-tyrosyl-D-alanyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

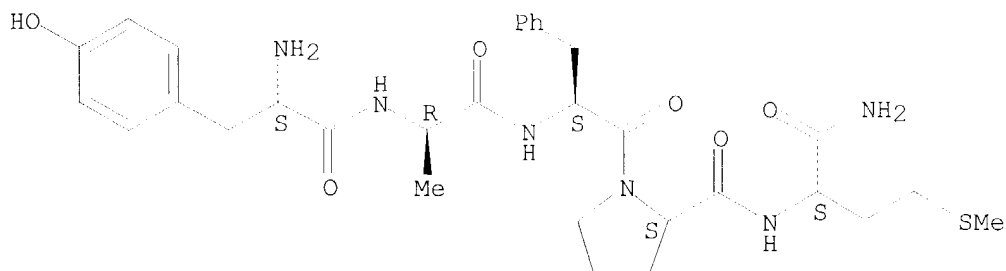
Absolute stereochemistry.



RN 83936-23-6 HCAPLUS

CN Dermorphin, 4-deglycine-5-de-L-tyrosine-7-L-methioninamide- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

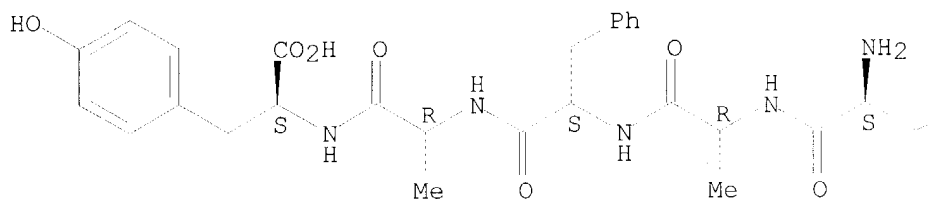


RN 100817-40-1 HCAPLUS

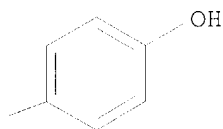
RN	108617-49-1	NON-ES
CN	Dormorhin,	4-D-alanine-6-de-L-proline-7-de-L-serinamide-
	(NAME)	(9CI) (CA INDEX

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L28 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1985:572492 HCAPLUS

DOCUMENT NUMBER: 103:172492

TITLE: Effect of a  $\beta$ -casomorphin analog on ion transport  
in rabbit ileum: evidence for a cholinergic mediation

AUTHOR(S):               Hautefeuille, M.; **Brantl, V.**; Dumontier, A.  
                              M.; Desjeux, J. F.

CORPORATE SOURCE: Unite Rech. Diabete Nutr. Enfant, CHU Villemin, Paris, 75010, Fr.

SOURCE: Regulatory Peptides (1985), (Suppl. 4), 219-20

CODEN: REPPDY; ISSN: 0167-0115

DOCUMENT TYPE: Journal

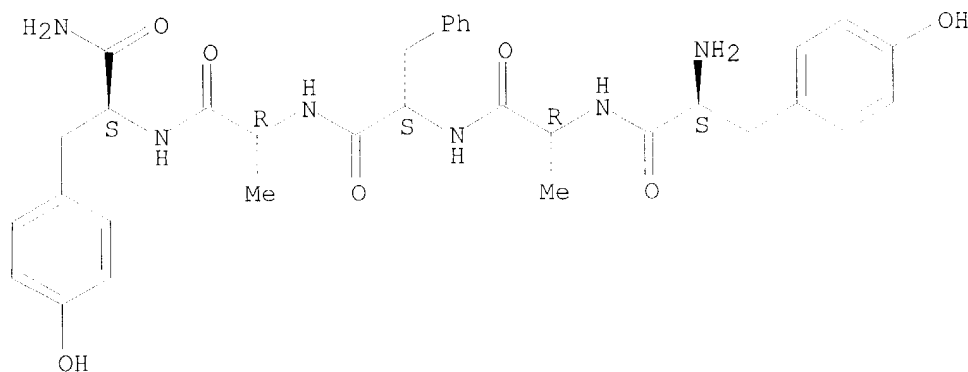
LANGUAGE: English

AB Ionic transport, as measured by the short-circuit current, by rabbit ileum preps. was inhibited by the  $\beta$ -casomorphin analog 4027 (Tyr-D-Ala-Phe-D-Ala-Tyr-NH<sub>2</sub>) [98815-38-4], and this response was prevented by the opiate antagonist naloxone. In this preparation, ionic transport was also inhibited by atropine, indicating the presence of cholinergic release. The effects of sequential adms. of 4027, naloxone, and atropine in different orders suggested that the **intestinal** ionic transport system involved an opioid receptor, a cholinergic agonist,

and an acetylcholine-sensitive epithelial layer. Evidently, 4027 suppressed a tonic cholinergic release, and the effect of 4027 was inhibited by naloxone at the opioid receptor site. Both 4027 and atropine acted at the enterocyte level.

CC 2-5 (Mammalian Hormones)  
 ST ileum ion transport casomorphin analog; receptor opioid ileum ion transport; cholinergic casomorphin analog ion transport ileum  
 IT Receptors  
 RL: BIOL (Biological study)  
 (for opiates, of ileum, in ion transport response to casomorphin analog)  
 IT Electrolytes  
 (transport of, by ileum, casomorphin analog inhibition of, cholinergic and opioid mechanisms for)  
 IT Receptors  
 RL: BIOL (Biological study)  
 (cholinergic, of **intestine** ileum, in ion transport response to casomorphin analog)  
 IT Opiates and Opioids  
 RL: BIOL (Biological study)  
 (endogenous, receptors for, of ileum, in ion transport response to casomorphin analog)  
 IT **Intestine**, metabolism  
 (ileum, ion transport by, casomorphin analog inhibition of, cholinergic and opioid mechanisms for)  
 IT **98815-38-4**  
 RL: BIOL (Biological study)  
 (ion transport by ileum inhibition by, cholinergic and opioid mechanisms for)  
 IT **98815-38-4**  
 RL: BIOL (Biological study)  
 (ion transport by ileum inhibition by, cholinergic and opioid mechanisms for)  
 RN 98815-38-4 HCAPLUS  
 CN L-Tyrosinamide, L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1985:482014 HCAPLUS  
 DOCUMENT NUMBER: 103:82014  
 TITLE: Novel opioid peptides derived from mitochondrial cytochrome b: cytochromes

AUTHOR(S): **Brantl, Victor**; Gramsch, Christian;  
Lottspeich, Friedrich; Henschen, Agnes; Jaeger, Karl  
Heinz; Herz, Albert

CORPORATE SOURCE: Boehringer Ingelheim K.-G., Ingelheim, D-6507, Fed.  
Rep. Ger.

SOURCE: European Journal of Pharmacology (1985), 111(2), 293-4  
CODEN: EJPHAZ; ISSN: 0014-2999

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The opioid activities of cytochromin-4 (Tyr-Pro-Phe-Thr)(I) and  
cytochromin-5 (Tyr-Pro-Phe-Thr-Ile) were lower than those of  
 $\beta$ -casomorphines or normorphine in the guinea pig ileum assay. The  
cytochromins were isolated from Haem-Uvocal, which was obtained by  
treatment of bovine blood with **gastrointestinal** enzymes. I  
represents fragment 345-348 from mitochondrial cytochrome b.

CC 2-5 (Mammalian Hormones)

ST opioid cytochrome b fragment; cytochromin opioid

IT Nomenclature, new natural products  
(cytochromin-4 (peptide))

IT Nomenclature, new natural products  
(cytochromin-5 (peptide))

IT Blood  
(enzymic hydrolyzates, cytochromins isolation from, opioid activity  
of)

IT Opiates and Opioids  
RL: BIOL (Biological study)  
(peptides, cytochromins-4 and -5 as, from cytochrome b)

IT **9035-37-4D**, fragments **97730-74-0 97730-75-1**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(opioid activity of)

IT **9035-37-4D**, fragments **97730-74-0 97730-75-1**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(opioid activity of)

RN 9035-37-4 HCAPLUS

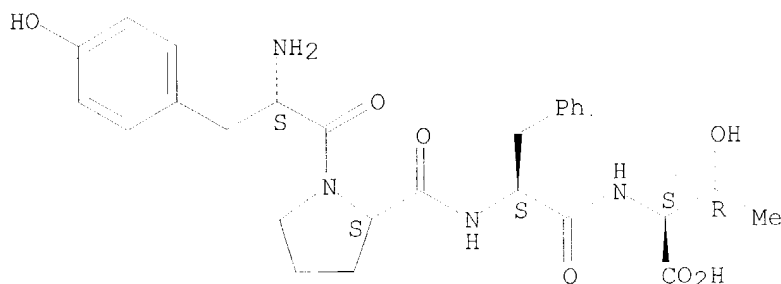
CN Cytochrome b (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 97730-74-0 HCAPLUS

CN L-Threonine, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

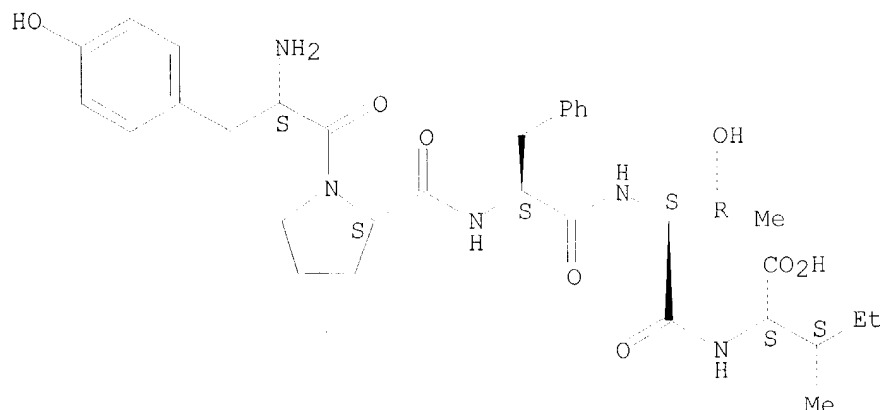
Absolute stereochemistry.



RN 97730-75-1 HCAPLUS

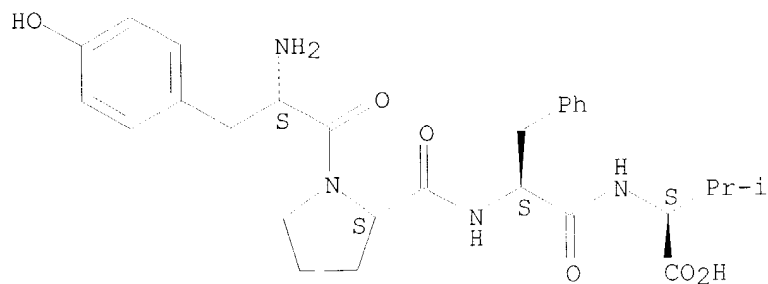
CN L-Isoleucine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-threonyl- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



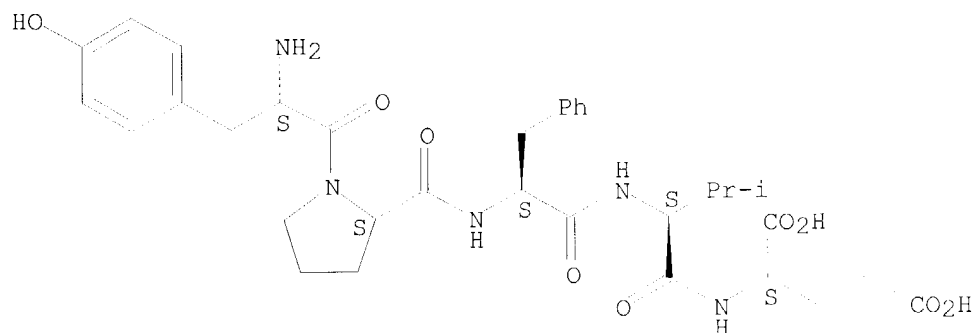
L28 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1985:110584 HCAPLUS  
 DOCUMENT NUMBER: 102:110584  
 TITLE: Novel opioid peptides derived from human  
 $\beta$ -casein: human  $\beta$ -casomorphins  
 AUTHOR(S): Brantl, Victor  
 CORPORATE SOURCE: Dep. Med., Boehringer Ingelheim K.-G., Ingelheim am  
 Rhein, D-6507, Fed. Rep. Ger.  
 SOURCE: European Journal of Pharmacology (1984), 106(1),  
 213-14  
 CODEN: EJPHAZ; ISSN: 0014-2999  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Human  $\beta$ -casomorphins 4 (Tyr-Pro-Phe-Val) and 5 (Tyr-Pro-Phe-Val-Glu)  
 were less potent than the corresponding bovine  $\beta$ -casomorphin 4  
 (Tyr-Pro-Phe-Pro) and 5 (Tyr-Pro-Phe-Pro-Gly) in inhibiting the  
 contraction of the guinea pig ileum induced by elec. stimulation.  
 CC 13-6 (Mammalian Biochemistry)  
 ST casomorphin ileum contraction  
 IT **Intestine**  
 (ileum, contraction of,  $\beta$ -casomorphins 4 and 5 of human inhibition  
 of)  
 IT Muscle  
 (smooth, contraction of,  $\beta$ -casomorphins 4 and 5 of human  
 inhibition of)  
 IT **94664-03-6 94664-04-7**  
 RL: BIOL (Biological study)  
 (ileum contraction inhibition by)  
 IT **94664-03-6 94664-04-7**  
 RL: BIOL (Biological study)  
 (ileum contraction inhibition by)  
 RN 94664-03-6 HCAPLUS  
 CN L-Valine, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 94664-04-7 HCAPLUS  
 CN L-Glutamic acid, L-tyrosyl-L-prolyl-L-phenylalanyl-L-valyl- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1983:540411 HCAPLUS  
 DOCUMENT NUMBER: 99:140411  
 TITLE: Pharmacologically active peptides and medicaments  
 containing them  
 INVENTOR(S): **Brantl, Victor**; Henschen, Agnes;  
 Teschemacher, Hansjoerg; Lottspeich, Friedrich  
 PATENT ASSIGNEE(S): Fed. Rep. Ger.  
 SOURCE: U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 229,577.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 4  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4390527	A	19830628	US 1981-258617	19810429
DE 2936099	A1	19810402	DE 1979-2936099	19790906
BR 8008818	A	19810623	BR 1980-8818	19800904
JP 56501648	T2	19811112	JP 1980-502020	19800904
JP 03069920	B4	19911105		
US 4681871	A	19870721	US 1981-229577	19810122
DK 8101998	A	19810505	DK 1981-1998	19810505
DK 160316	B	19910225		
DK 160316	C	19910729		

US 4555403 A 19851126 US 1983-507807 19830624  
 PRIORITY APPLN. INFO.: DE 1979-2936099 19790906  
 US 1981-229577 19810122  
 DE 1979-2921216 19790525  
 WO 1980-DE72 19800520  
 WO 1980-DE126 19800904  
 US 1981-258617 19810429

AB  $\beta$ -Casomorphin tri- to nonapeptide analogs from H-Tyr-X-X1-OH to H-Tyr-X-X1-Pro-X2-Pro-Leu-Pro-X3-OH (X = D-Pro, D-Ala, D-Thr, D-Val; X1 = Phe, Pro, Tyr; X2 = Gly, Pro, Tyr; X3 = Asn, Pro, Ile) were prepared as opiates. Thus, H-Tyr-X4-Phe-Pro-Gly-OMe (X4 = D-Ala, D-Pro) were prepared by conventional solution methods using mixed anhydride peptide coupling reactions. D-Ala2- $\beta$ -casomorphin exhibited opiate activity in the guinea pig **intestine** test after 120 min exposure to enzymes, whereas  $\beta$ -casomorphin was inactive after 30 min.

IC A61K037-00; C07C103-52  
 NCL 424177000  
 CC 34-3 (Amino Acids, Peptides, and Proteins)  
 Section cross-reference(s): 63  
 ST casomorphin analog prepn opiate  
 IT Opiates and Opioids  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 ( $\beta$ -casomorphin analogs)

IT **501-53-1**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (benzyloxycarbonylation by, of D-alanine)

IT **338-69-2**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (benzyloxycarbonylation of)

IT **5680-79-5**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with dipeptide derivative)

IT **7669-64-9**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with glycine Me ester)

IT **29713-96-0**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with tetrapeptide Me esters)

IT **6404-31-5**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with tripeptide Me ester)

IT **77434-40-3P 79706-54-0P 79706-55-1P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and hydrogenolysis of)

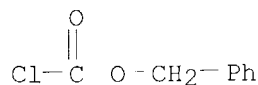
IT **79805-24-6DP**, analogs  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and opiate activity of)

IT **26607-51-2P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and peptide coupling of, with tripeptide Me ester)

IT **79706-56-2P 79706-57-3P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and peptide coupling of, with tyrosine derivative)

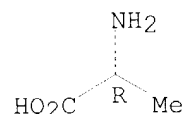
IT **77434-41-4P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and peptide coupling of, with D-alanine or D-proline derivative)

IT 79706-52-8P 79706-53-9P 82289-40-5P  
 83936-22-5P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 IT 501-53-1  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (benzyloxycarbonylation by, of D-alanine)  
 RN 501-53-1 HCAPLUS  
 CN Carbonochloridic acid, phenylmethyl ester (9CI) (CA INDEX NAME)

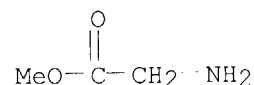


IT 338-69-2  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (benzyloxycarbonylation of)  
 RN 338-69-2 HCAPLUS  
 CN D-Alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 5680-79-5  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with dipeptide derivative)  
 RN 5680-79-5 HCAPLUS  
 CN Glycine, methyl ester, hydrochloride (6CI, 8CI, 9CI) (CA INDEX NAME)

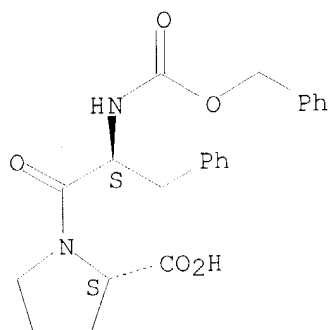


● HCl

IT 7669-64-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (peptide coupling of, with glycine Me ester)  
 RN 7669-64-9 HCAPLUS  
 CN L-Proline, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





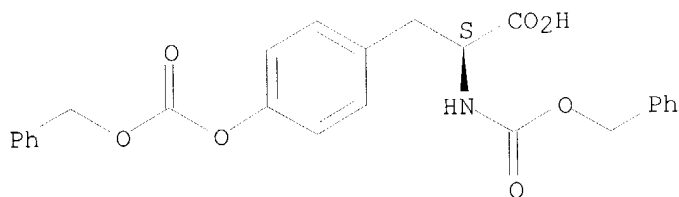
IT 29713-96-0

RL: RCT (Reactant); RACT (Reactant or reagent)  
(peptide coupling of, with tetrapeptide Me esters)

RN 29713-96-0 HCAPLUS

CN L-Tyrosine, N-[(phenylmethoxy)carbonyl]-, phenylmethyl carbonate (ester)  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



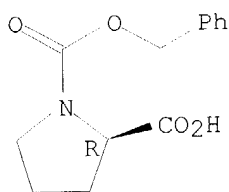
IT 6404-31-5

RL: RCT (Reactant); RACT (Reactant or reagent)  
(peptide coupling of, with tripeptide Me ester)

RN 6404-31-5 HCAPLUS

CN 1,2-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl) ester, (2R)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry. Rotation (+).



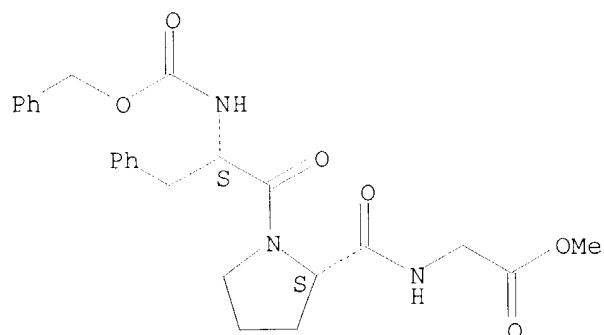
IT 77434-40-3P 79706-54-0P 79706-55-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation and hydrogenolysis of)

RN 77434-40-3 HCAPLUS

CN Glycine, N-[1-[N-[(phenylmethoxy)carbonyl]-L-phenylalanyl]-L-prolyl]-,  
methyl ester (9CI) (CA INDEX NAME)

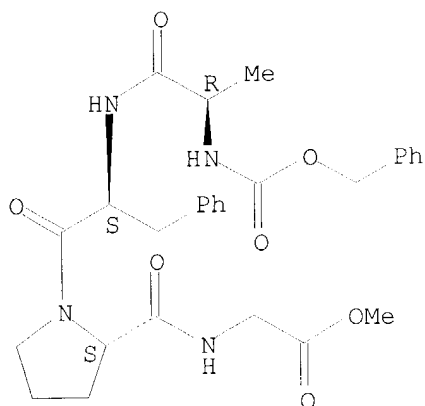
Absolute stereochemistry.



RN 79706-54-0 HCAPLUS

CN Glycine, N-[1-[N-[N-[(phenylmethoxy)carbonyl]-D-alanyl]-L-phenylalanyl]-L-prolyl]-, methyl ester (9CI) (CA INDEX NAME)

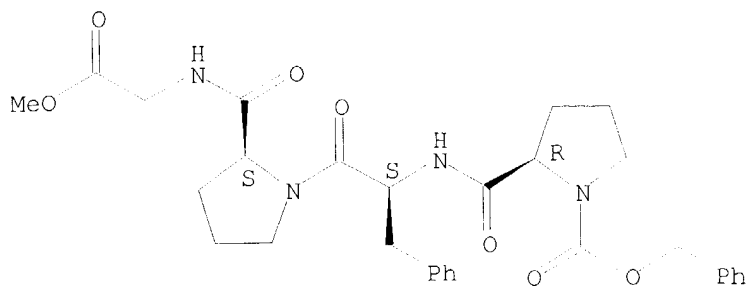
Absolute stereochemistry.



RN 79706-55-1 HCAPLUS

CN Glycine, N-[1-[N-[1-[(phenylmethoxy)carbonyl]-D-prolyl]-L-phenylalanyl]-L-prolyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 79805-24-6DP, analogs

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation and opiate activity of)

RN 79805-24-6 HCAPLUS  
 CN  $\beta$ -Casomorphin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

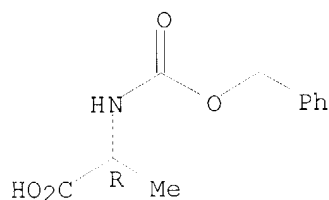
IT **26607-51-2P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation and peptide coupling of, with tripeptide Me ester)

RN 26607-51-2 HCAPLUS

CN D-Alanine, N-[(phenylmethoxy)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



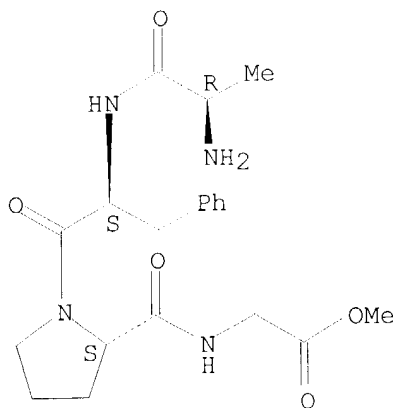
IT **79706-56-2P 79706-57-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation and peptide coupling of, with tyrosine derivative)

RN 79706-56-2 HCAPLUS

CN Glycine, N-[1-(N-D-alanyl-L-phenylalanyl)-L-prolyl]-, methyl ester (9CI)  
 (CA INDEX NAME)

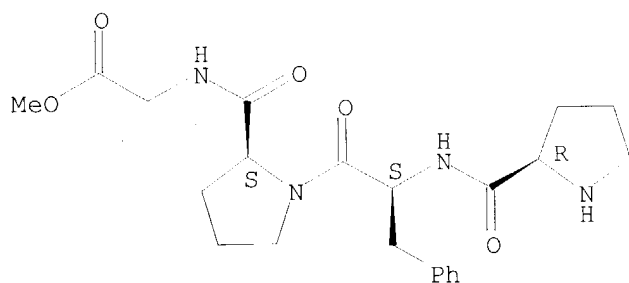
Absolute stereochemistry.



RN 79706-57-3 HCAPLUS

CN Glycine, N-[1-(N-D-prolyl-L-phenylalanyl)-L-prolyl]-, methyl ester (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.



IT 77434-41-4P

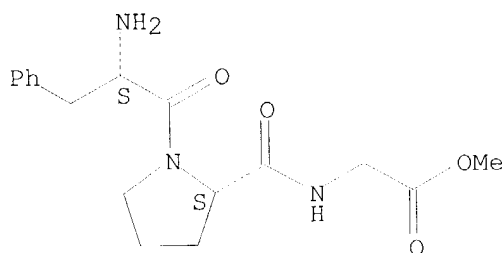
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and peptide coupling of, with D-alanine or D-proline derivative)

RN 77434-41-4 HCAPLUS

CN Glycine, L-phenylalanyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

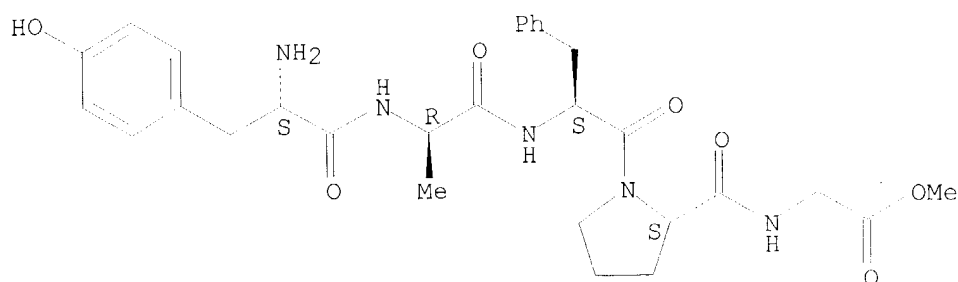
Absolute stereochemistry. Rotation (-).

IT 79706-52-8P 79706-53-9P 82289-40-5P  
83936-22-5PRL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of)

RN 79706-52-8 HCAPLUS

CN Glycine, N-[1-[N-(N-L-tyrosyl-D-alanyl)-L-phenylalanyl]-L-prolyl]-, methyl ester (9CI) (CA INDEX NAME)

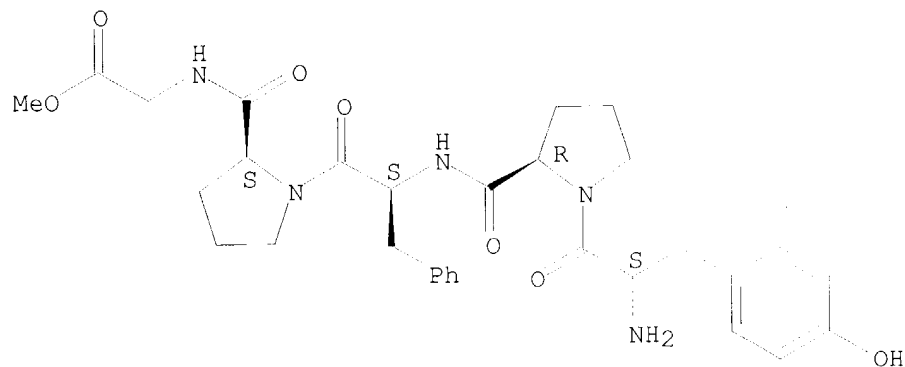
Absolute stereochemistry.



RN 79706-53-9 HCAPLUS

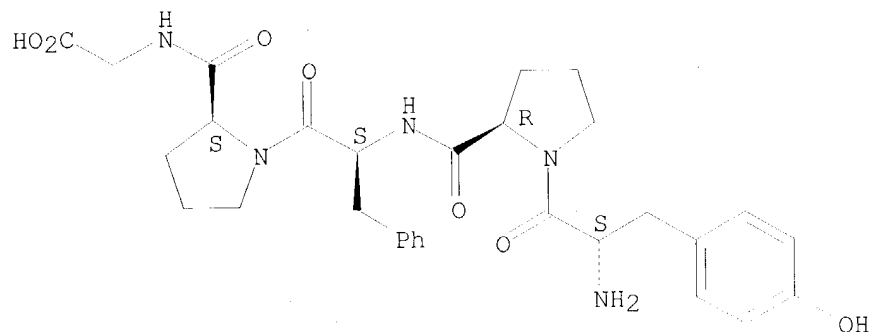
CN Glycine, N-[1-[N-(1-L-tyrosyl-D-prolyl)-L-phenylalanyl]-L-prolyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



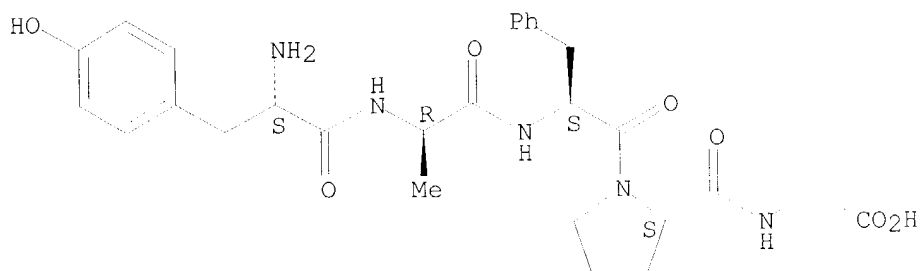
RN 82289-40-5 HCAPLUS  
 CN Glycine, N-[1-[N-(1-L-tyrosyl-D-prolyl)-L-phenylalanyl]-L-prolyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.



RN 83936-22-5 HCAPLUS  
 CN Dermorphin, 4-deglycine-5-de-L-tyrosine-7-glycine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 1983:416934 HCAPLUS  
 DOCUMENT NUMBER: 99:16934  
 TITLE: Effect of  $\beta$ -casomorphins on somatostatin release

in dogs  
AUTHOR(S): Schusdziarra, V.; Schick, R.; De la Fuente, A.;  
Holland, A.; Brantl, V.; Pfeiffer, E. F.  
CORPORATE SOURCE: Dep. Int. Med. I, Univ. Ulm, Ulm, Fed. Rep. Ger.  
SOURCE: Endocrinology (1983), 112(6), 1948-51  
CODEN: ENDOAO; ISSN: 0013-7227  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The effects of orally administered  $\beta$ -casomorphins ( $\beta$ -CM) and  
methionine-enkephalin (met-enkephalin) [58569-55-4] on  
postprandial plasma somatostatin [51110-01-1]-like  
immunoreactivity (SLI) were assessed in conscious dogs. The intragastric  
instillation of a liver extract-sucrose test meal containing 12 mg  $\beta$ -CM or  
10 mg met-enkephalin, resp., augmented the postprandial rise of peripheral  
vein plasma SLI levels. This effect was inhibited by the addnl.  
administration of the specific opiate-receptor antagonist, naloxone. When  
liver extract and sucrose was dissolved in fresh bovine milk the increase of  
plasma SLI levels was greater than liver extract and sucrose dissolved in  
water. This milk-induced augmentation of SLI levels was also reduced by  
naloxone. Since these opiate-active compds. have an influence on insulin  
release when given i.v., the effect of  $\beta$ -CM-7 [ 72122-62-4  
],  $\beta$ -CM-5 [ 72122-63-5],  $\beta$ -CM-4 [ 74171-19-0  
],  $\beta$ -CM-4-amide [ 74135-04-9], and met-enkephalin on SLI  
levels was assessed during i.v. infusion at a rate of 1 nmol/kg/h during  
an i.v. background infusion of a glucose-amino acid mixture. The infusion of  
 $\beta$ -CM-5 increased peripheral vein SLI levels, whereas the infusion of  
met-enkephalin decreased SLI levels.  $\beta$ -CM-7,  $\beta$ -CM-4, and  
 $\beta$ -CM-4-amide had no effect on plasma SLI levels at the dose employed.  
Thus, in dogs, the ingestion of opiate-active peptide stimulates  
postprandial SLI release, indicating that nutrient-contained opiate-active  
material (exorphins) might participate in the regulation of postprandial  
gastrointestinal endocrine function.  
CC 2-5 (Mammalian Hormones)  
Section cross-reference(s): 18  
ST casomorphin somatostatin plasma; enkephalin somatostatin plasma  
IT Opiates and Opioids  
RL: BIOL (Biological study)  
(somatostatin of blood plasma response to dietary)  
IT Blood plasma  
(somatostatin of,  $\beta$ -casomorphins and enkephalin dietary  
administration effect on)  
IT 51110-01-1  
RL: BIOL (Biological study)  
(of blood plasma,  $\beta$ -casomorphins and enkephalin dietary  
administration effect on)  
IT 72122-62-4 72122-63-5 74135-04-9  
74171-19-0  
RL: BIOL (Biological study)  
(somatostatin of blood plasma response to dietary)  
IT 58569-55-4  
RL: BIOL (Biological study)  
(somatostatin of blood plasma response to dietary,  $\beta$ -casomorphins  
in relation to)  
IT 51110-01-1  
RL: BIOL (Biological study)  
(of blood plasma,  $\beta$ -casomorphins and enkephalin dietary  
administration effect on)  
RN 51110-01-1 HCAPLUS  
CN Somatostatin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

IT 72122-62-4 72122-63-5 74135-04-9

74171-19-0

RL: BIOL (Biological study)

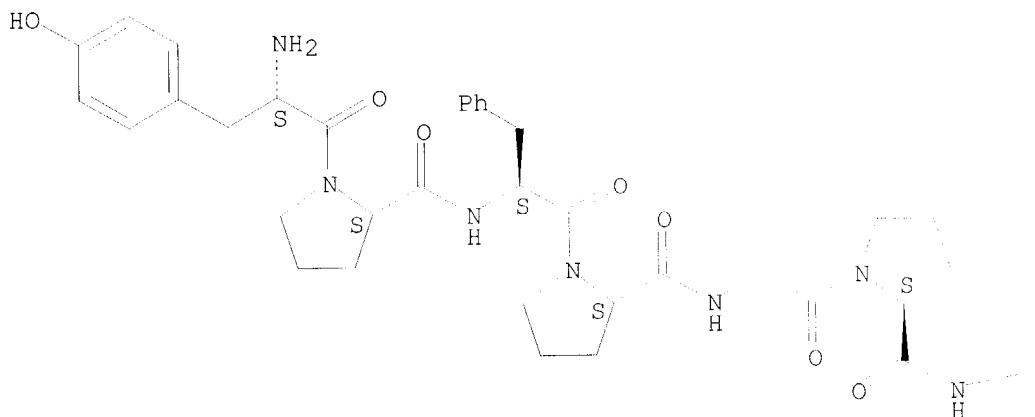
(somatostatin of blood plasma response to dietary)

RN 72122-62-4 HCAPLUS

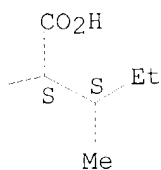
CN L-Isoleucine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolyl-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

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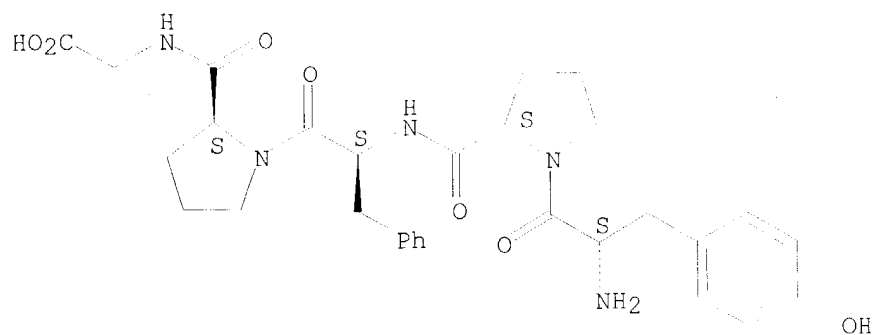
PAGE 1-B



RN 72122-63-5 HCAPLUS

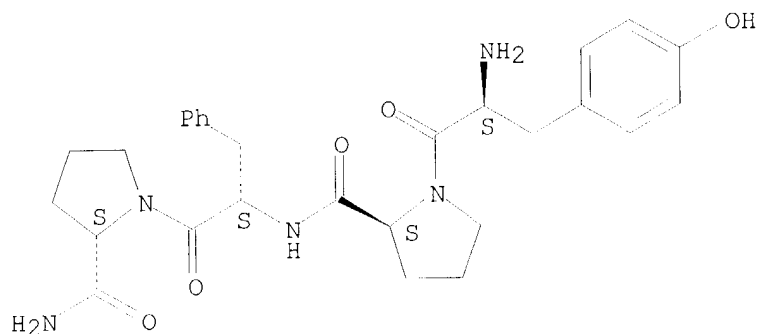
CN Glycine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



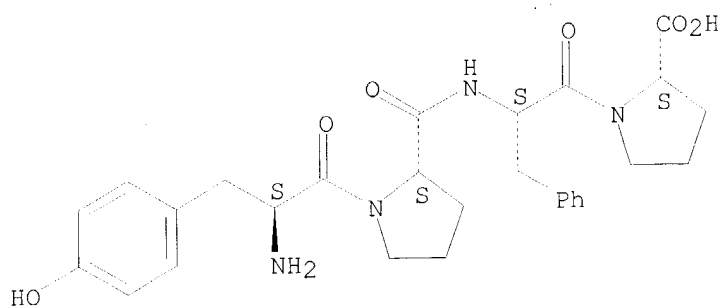
RN 74135-04-9 HCAPLUS  
 CN L-Prolinamide, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 74171-19-0 HCAPLUS  
 CN L-Proline, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 58569-55-4

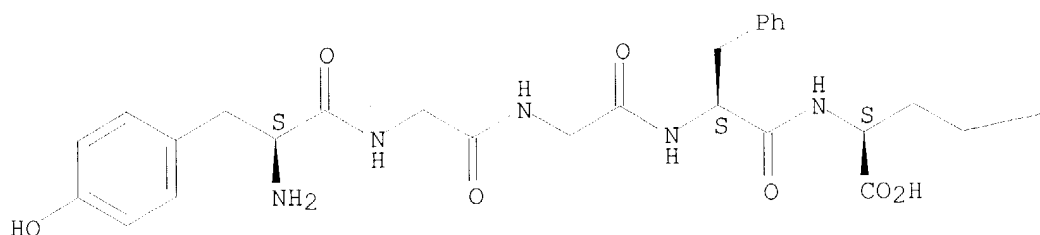
RL: BIOL (Biological study)  
 (somatostatin of blood plasma response to dietary,  $\beta$ -casomorphins  
 in relation to)

RN 58569-55-4 HCAPLUS  
 CN 1-5-Adrenorphin (human) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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PAGE 1-B

SMe

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ACCESSION NUMBER: 1982:484549 HCAPLUS

DOCUMENT NUMBER: 97:84549

TITLE: Isolation of pharmacologically active peptides by high-pressure liquid chromatography (HPLC)

AUTHOR(S): Brantl, Victor

CORPORATE SOURCE: Abt. Neuropharmakol., Max-Planck-Inst. Psychiatrie, Munich, D-8000/40, Fed. Rep. Ger.

SOURCE: High Perform. Liq. Chromatogr. Protein Pept. Chem., Proc. Int. Symp. (1981), 365-84. Editor(s): Lottspeich, Friedrich; Henschen, Agnes; Hupe, Klaus-Peter. de Gruyter: Berlin, Fed. Rep. Ger. CODEN: 48BDAM

DOCUMENT TYPE: Conference

LANGUAGE: English

AB A material which displayed opioid activity in the guinea pig ileum longitudinal muscle-myenteric plexus preparation was extracted from an enzymic bovine casein digest into CHCl<sub>3</sub>-MeOH. The extract was roughly purified by absorption/desorption procedures by use of charcoal and Amberlite XAD 2 resin as adsorbents. The material was then submitted to 5 HPLC purification steps on  $\mu$ Bondapak C18 and  $\mu$ Porasil. In the last step, a single compound was obtained which contained a pure heptapeptide with the sequence Tyr-Pro-Phe-Pro-Gly-Pro-Ile. This opioid peptide, which is highly resistant towards proteolytic enzymes, was a fragment of bovine  $\beta$ -casein. In view of its origin from  $\beta$ -casein and its opiate activity, this peptide was named  $\beta$ -casomorphin-7 [ 72122-62-4 ]. Detailed information concerning the purification procedures, the purity criteria, structure anal., and some pharmacol. properties of  $\beta$ -casomorphin-7 and its smaller fragments are described.

CC 1-1 (Pharmacology)

ST opioid high pressure liq chromatog; ileum opioid peptide purifn

IT Enkephalins

RL: PUR (Purification or recovery); PREP (Preparation)

(purification of, of guinea pig ileum by high-performance liquid chromatog.)

IT Chromatography, column and liquid

(high-pressure, of opioid peptides)

IT Intestine, composition

(ileum, opioids purification in, of guinea pig by high-performance liquid chromatog.)

IT 466-97-7P 58569-55-4P 72122-62-4P

72122-63-5P 74171-19-0P 77434-43-6P

RL: PUR (Purification or recovery); PREP (Preparation)

(purification of, of guinea pig ileum by high-performance liquid chromatog.)

IT 466-97-7P 58569-55-4P 72122-62-4P

72122-63-5P 74171-19-0P 77434-43-6P

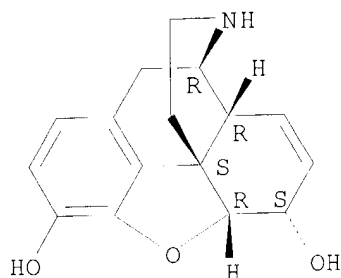
RL: PUR (Purification or recovery); PREP (Preparation)

(purification of, of guinea pig ileum by high-performance liquid chromatog.)

RN 466-97-7 HCAPLUS

CN Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-, (5 $\alpha$ ,6 $\alpha$ )- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

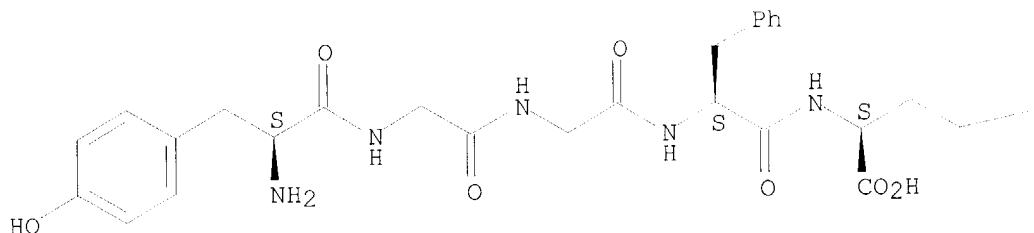


RN 58569-55-4 HCAPLUS

CN 1-5-Adrenorphin (human) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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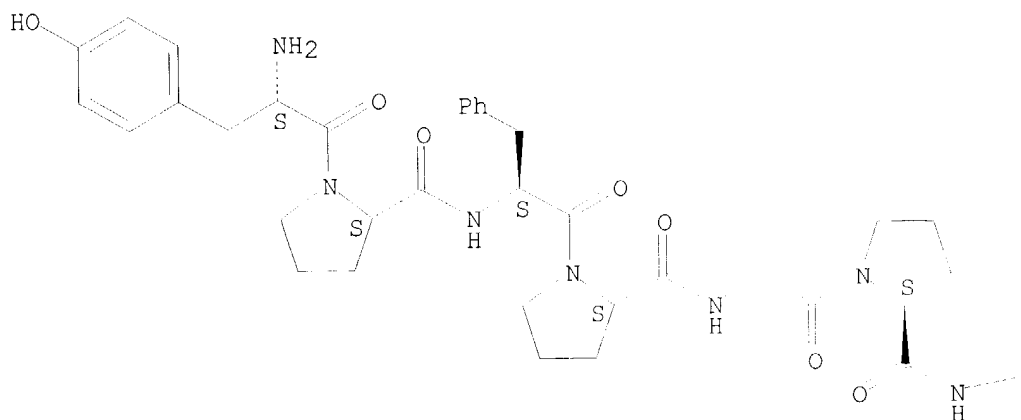
SMe

RN 72122-62-4 HCAPLUS

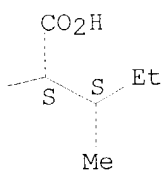
CN L-Isoleucine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolylglycyl-L-prolyl-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

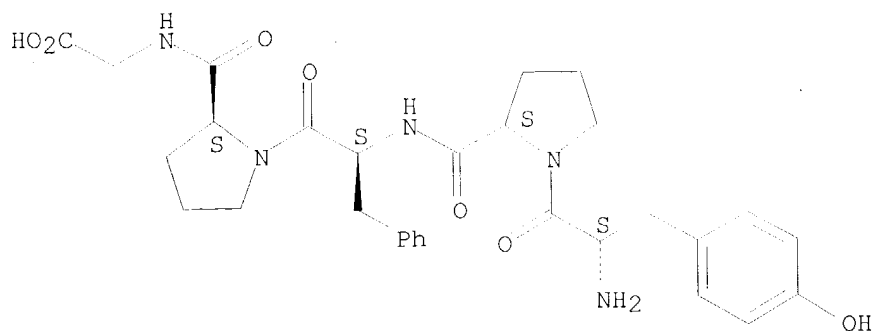


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RN 72122-63-5 HCAPLUS  
 CN Glycine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolyl- (9CI) (CA INDEX  
 NAME)

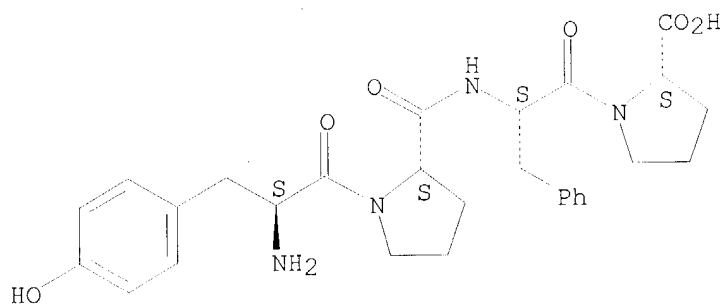
Absolute stereochemistry. Rotation (-).



RN 74171-19-0 HCAPLUS

CN L-Proline, L-tyrosyl-L-prolyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 77434-43-6 HCAPLUS

CN L-Proline, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

